(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 May 2003 (01.05.2003)

PCT

(10) International Publication Number
WO 03/034938 A2

(51) International Patent Classification[7]: A61F

(21) International Application Number: PCT/US02/34344

(22) International Filing Date: 25 October 2002 (25.10.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/343,732 25 October 2001 (25.10.2001) US

(71) Applicant *(for all designated States except US)*: WISCONSIN ALUMNI RESEARCH FOUNDATION [US/US]; 614 Walnut Street, Madison, WI 53707-7365 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: WOLFF, Matthew, R. [US/US]; 1332 North High Point Road, Middleton, WI 53562 (US).

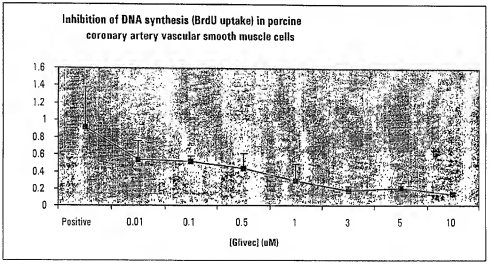
(74) Agents: LEONE, Jos, T. et al.; DeWitt Ross & Stevens S.C., 8000 Excelsior Drive, Madison, WI 53717-1914 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: VASCULAR STENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND METHOD OF USING SAME



(57) Abstract: Disclosed is a device, such as a cardiovascular stent, autologous venous/arterial graft, prosthetic venous/arterial graft, vascular catheter, or vascular shunt, for stenting a blood vessel. The device has coated thereon, adsorbed thereto, impregnated therein, or covalently or ionically bonded thereto an amount of a protein tyrosine kinase inhibitor. The protein tyrosine kinase inhibitor proliferation of vascular smooth muscle cells in an area within a blood vessel immediately adjacent to and/or proximal to the device, while simultaneously not inhibiting the proliferation of vascular intimal cells. A corresponding method of using the device to stent blood vessels is also disclosed.

WO 03/034938 A2

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

VASCULAR STENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND METHOD OF USING SAME

Matthew R. Wolff

RELATED APPLICATION

Priority is hereby claimed to provisional application Serial No. 60/343,732, filed October 25, 2001, which provisional application is incorporated herein by reference.

FIELD OF THE INVENTION

The invention is directed to methods of selectively inhibiting the proliferation of vascular smooth muscle cells (VSMCs) following vascular injury or surgical interventions such as percutaneous revascularization, without inhibiting the prolifration of endothelial cells. Specifically, the invention is directed to the use of protein tyrosine kinase inhibitors, preferably those that inhibit the Bcr-Abl tyrosine kinase, and most preferably 4-{(4-methyl-1-piperazinyl)methyl}-N-{4-methyl-3-{{4-(3-pyrimidinyl}amino}-phenyl}benzamide methane sulfonate, coated onto vascular stents, native grafts, or prosthetic vascular grafts, to prevent the proliferation of VSMCs selectively, while not adversely affecting the proliferation of endothelial cells.

BACKGROUND

Arteriosclerosis is a class of diseases characterized by the thickening and hardening of the arterial walls of blood vessels. Although all blood vessels are susceptible to this serious degenerative condition, the aorta and the coronary arteries serving the heart are most often affected. Arteriosclerosis is of profound clinical importance since it can increase the risk of heart attacks, myocardial infarctions, strokes, and aneurysms.

The traditional treatment for arteriosclerotic vessels currently includes vascular recanalization procedures for less-serious blockages and coronary bypass surgery for major blockages. Where possible, vascular recanalization is much preferred to coronary bypass because it is a far less invasive procedure. Vascular recanalization procedures involve using

intravascular devices threaded through blood vessels to the obstructed site, including for example, percutaneous transluminal coronary balloon angioplasty (PTCA), also known as balloon angioplasty. Balloon angioplasty uses a catheter with a balloon tightly packed onto its tip. When the catheter reaches the obstruction, the balloon is inflated, and the atherosclerotic plaques are compressed against the vessel wall. A serious shortcoming of this and other intravascular procedures, however, is that in a significant number of treated individuals, some or all of the treated vessels restenose (that is, the vessels again narrow). This generally occurs in a relatively brief time period, roughly less than six months, after treatment. The restenosis is thought to be due in part to mechanical injury to the walls of the blood vessels caused by the balloon catheter or other intravascular device.

The walls of most blood vessels are composed of three distinct layers, or tunics, surrounding a central tubular opening, the vessel lumen. The innermost layer that lines the vessel lumen is called the tunica intima. The middle layer, the tunica media, consists mostly of circularly arranged smooth muscle cells and connective tissue fibers. In a non-injured vessel, the smooth muscle cells are generally not actively dividing. The outmost layer of the blood vessel wall, the tunica adventitia, is composed largely of collagen fibers that protect inner layers and gives the blood vessel structural integrity. Mechanical injury, resulting in damage to the tunica intima, initiates a cascade of events, including the release of chemicals such as platelet-derived growth factors (PDGF). This cascade prompts the migration and proliferation of vascular smooth muscle cells (VSMCs) at the site of injury. The accumulation of VSMCs at the site of injury narrows the diameter of the vessel lumen, thereby again putting the patient in danger of having a heart attack, stroke, etc.

Several methods for inhibiting smooth muscle cell proliferation following the use of an intravascular device have been reported in the patent literature. These include administering anti-proliferative agents such as cell cycle inhibitors and anti-coagulant agents (either by local or systemic delivery systems). Delivery of these agents systemically, however, has required dosages that cause unacceptable side-effects or are prohibitively expensive. Local delivery of agents, for example heparin, as described in U.S. Pat. No. 4,824,436, has proven ineffective in inhibiting restenosis due in part to inadequate residence time of the

active agent at the site of injury. Cell cycle inhibitors such as taxol, which do not react covalently and therefore require prolonged residence time for effectiveness, suffer from similar problems. Moreover, prolonging residence times to increase the effectiveness of such treatments is also likely to present increased risks of toxicity.

Other methods reported for inhibiting VSMC proliferation involve local delivery of active agents contained in a sustained-release formulation. For example, U.S. Pat. No. 5,171,217 describes agents contained within a physiologically compatible, biodegradable polymeric microparticle. This formulation is delivered locally to the site of injury such that the agents are released from the arterial wall for 72 hours or more. In contrast, U.S. Pat. No. 6,281,225 describes the local, but non-sustained-release administration of DNA alkylating agents to prevent VSMC proliferation.

Another method for inhibiting smooth muscle cell proliferation involves administering photochemically-activated agents by local delivery systems. For example, U.S. Pat. No. 5,354,774 describes locally delivering 8-methoxypsoralen to the site of injury and then activating a photodynamic reaction using a visible light source.

Yet another approach to prevent proliferation of VSMCs is the use of radiation-emitting catheters or guide wires. These radioactive devices cause damage to nucleic acid, thus inhibiting replication and thereby inhibiting smooth muscle cell proliferation.

All of the above-described methods suffer from certain drawbacks. For example, sustained release formulations require an added level of complexity, namely incorporation of the agent on or within a sustained release formulation. Photodynamic therapy requires both local delivery of the photo-active agent and the use of a complex intravascular light source. Delivery of a radiation dose requires the presence of a radiologist and presents exposure hazards to the attending personnel, as well as material storage, handling, and disposal complications.

Treated coronary stents now on the market or in clinical trials also suffer from the distinct drawback that they inhibit the proliferation of endothelial cells. This contributes to thrombosis in the vicinity of deployed stent. Thrombosis has been observed in human clinical trials when using stents coated with either taxol or rapamycin. To prevent such thrombosis, the clinical patients have had to undergo a two- to three-month duration anti-coagulation treatment.

A need therefore exists for safe, simple, and straightforward method for inhibiting VSMC proliferation at a site of injury following vascular recanalization procedures or other vascular injury, without inhibiting the proliferation of endothelial cells. The ideal solution should be non-radioactive and require little or no retraining of medical personnel to implement.

Cellular signaling has become a major research theme in biology and medicine over the past twenty years. The complex pathways and protein components in signal transduction are emerging only slowly, but with increasing clarity. Over the last 15 years, the protein tyrosine kinases have been identified as key players in cellular regulation. They are involved in immune, endocrine, and nervous system physiology and pathology and thought to be important in the development of many cancers, most notably chronic myeloid leukemia. As such they serve as drug targets for many different diseases. A host of protein tyrosine kinases are known in the art. The attached Sequence List includes a non-exclusive sampling of the amino acid sequences of a number of such kinases.

As used herein, the term protein tyrosine kinases (PTKs) refers to any and all enzymes falling within the enzyme classification EC 2.1.7.112, without limitation. See the Sequence List, attached hereto, for various examples of PTKs. These enzymes catalyze the transfer of the gamma-phosphoryl group from ATP to the tyrosine hydroxyl moiety of a protein substrate. This family of kinases shares amino acid sequence homology with the serine/threonine kinase family. Although the number of tyrosine kinases being discovered is growing exponentially, molecular details pertaining to their substrate recognition, catalytic mechanism, and intra- and intermolecular regulation are still being elucidated.

As described in full below, the present inventors have found that inhibiting the action of PTKs selectively inhibits the proliferation of VSMCs.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph depicting porcine coronary vascular smooth muscle cell proliferation following stimulation with platelet-derived growth factor (PDGF) in the presence of increasing concentrations of STI-571.

FIG. 2 is a graph depicting porcine aortic endothelial cell proliferation following stimulation with vascular endothelial growth factor (VEGF) in the presence of increasing concentrations of STI-571.

FIG. 3 is a graph depicting inhibition of proliferation of human coronary artery vascular smooth muscle cells (hCASMC) by increasing concentrations of STI-571 ("Glivec"). Cells were counted after stimulation with 10% fetal bovine serum (FBS) for 48 hours, and data for each experiment was normalized to positive control wells containing FBS and no STI-571 ("Glivec"). Each point represents 18 to 21 wells from eight separate experiments, and is presented as the mean +/- the standard deviation.

FIG. 4 is a graph depicting inhibition of DNA synthesis in human coronary artery vascular smooth muscle cells (HCAVSMC) by STI-571 ("Glivec"). DNA synthesis was assayed by incorporation of BrdU after stimulation of coronary artery vascular smooth muscle cells by 10% FBS for 48 hours in the presence or absence (positive control) of STI-571 ("Glivec"). Data points represent 14 to 28 wells from two separate experiments, and are presented as the mean +/- the standard deviation.

FIG. 5 is a graph depicting inhibition of migration of human coronary artery vascular smooth muscle cells in response to STI-571 ("Glivec"). Migration was assayed by counting cells that migrated through a porous membrane (20 μm diameter pores) in 24 hours in response to stimulation with platelet-derived growth factor (PDGF-ββ). Data bars represent six membranes, and are presented as means normalized to control membranes (no STI-571) +/- the standard deviation.

FIG. 6 is a graph depicting the lack of any effect of STI-571 ("Glivec") on the proliferation of human coronary artery endothelial cells (hCAEC).

DETAILED DESCRIPTION OF THE INVENTION

Abbreviations and Definitions:

The following abbreviations and definitions are used throughout the specification and claims. Terms not specifically defined herein have their normal and accepted meaning within the field of cardiovascular medicine and/or physiology.

"BrdU" = 5-bromo-2'-deoxy-uridine triphosphate.

"DME" = Dulbecco's modified Eagle's media.

"FBS" = fetal bovine serum.

"JAK-2" = Janus-activated tyrosine kinases.

"MAPK" = mitogen-activated protein kinases.

"PDGF" = platelet-derived growth factor.

"Pharmaceutically-suitable salt" = any acid or base addition salt whose counter-ions are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial inhibitory effects inherent in the free base or free acid PTK inhibitor are not vitiated by side effects ascribable to the counter-ions. A host of pharmaceutically-suitable salts are well known in the pharmaceutical field. For active ingredients that are bases, all acid addition salts are useful as sources of the free base form even if the particular salt, per se, is desired only as an intermediate product as, for example, when the salt is formed only for purposes of purification, and identification, or when it is used as intermediate in preparing a pharmaceutically-suitable salt by ion exchange procedures. Pharmaceutically-suitable acid addition salts include, without limitation, those derived from mineral acids and organic acids, explicitly including hydrohalides, *e.g.*, hydrochlorides and hydrobromides, sulphates, phosphates, nitrates, sulphamates, acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methane-sulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates, quinates, and the like. In analogous fashion, for active ingredients that are acids, pharmaceutically-suitable base addition salts may be used. Base addition salts include, without limitation, those derived from alkali or alkaline earth metal bases or conventional organic bases, such as triethylamine, pyridine, piperidine, morpholine, N-methylmorpholine, and the like.

"PTCA" = percutaneous transluminal coronary balloon angioplasty.

"PTK" = protein tyrosine kinase; expressly defined herein as any and all enzymes falling within the enzyme classification EC 2.1.7.112, without limitation.

"PTK Inhibitor" = any compound or composition that selectively inhibits the catalytic activity of one or more protein tyrosine kinase inhibitors.

"STI-571" = 4-{(4-methyl-1-piperazinyl)methyl}-N-{4-methyl-3-{{4-(3-pyrimidinyl}amino}-phenyl}benzamide and pharmaceutically-suitable salts thereof. The methane-sulphonate salt is preferred. This compound has been given the trivial generic name "imatinib." As used herein, the term "STI-571" designates imatinib as either a free base or any pharmaceutically-suitable salt thereof, the mesylate salt being preferred. In the United States, it is marketed commercially by Novartis AG (Basel, Switzerland) under the registered trademark "Glivec" (U.S. T.M. Registration No. 2,478,196); it is also sold elsewhere around the world under the trademark "Gleevec."

"VEGF" = vascular endothelial growth factor.

"VSMC" = vascular smooth muscle cells.

Overview:

Treating arteriosclerosis with intravascular devices, including for example, ablative procedures, balloon catheters, or vascular stents is becoming increasingly popular as technology related to intravascular devices continues to improve. Approximately 1 million balloon angioplasty procedures alone are performed on an annual basis globally. These procedures, however, have a major shortcoming. In a significant number of cases the treated vessels re-occlude, or restenose, by six months post-treatment which requires the individual to undergo additional treatment. "Restenosis" refers to the stage at which the vessel lumen has decreased in diameter by about 50% or more as compared to the diameter of the vessel lumnen immediately following a vascular recanalization procedure.

The pathogenesis of restenosis is not well understood. It is believed to be due, in part, to recoil of the wall of the treated vessel. Additionally, it is hypothesized that vascular recanalization procedures used to treat diseases, such as arteriosclerosis, can cause mechanical injury at the site of recanalization. Without being limited to any particular mechanism of action, it is hypothesized that once intimal rupture occurs in the blood vessel a number of events begin to take place including the migration of monocytes to the

subendothelial layer of the intima and the release of mitogenic growth factors, including, for example, platelet-derived growth factor (PDGF), macrophage-derived growth factor (MDGF), and endothelial cell-derived growth factor (EDGF). These chemicals, and in particular PDGF, apparently play a role in inducing VSMC proliferation. This in turn produces substantial quantities of intercellular substances that accumulate within the vessel lumen, thereby narrowing its diameter.

A first embodiment of the present invention is therefore directed to a cardiovascular stent, autologous venous/arterial graft, prosthetic venous/arterial graft, vascular catheter or vascular shunt (collectively referred to herein as a "vascular device") that is coated with one or more compounds that selectively inhibit the proliferation of VSMCs at the point immediately adjacent to and proximal to the point of vascular injury. Specifically, the invention comprises a vascular device that has coated thereon, adsorbed thereto, impregnated therein, or covalently or ionically bonded thereto an amount of a protein tyrosine kinase (PTK) inhibitor. It is preferred that the compound specifically inhibit the Bcr-Abl tyrosine kinase, the constituitive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality found in chronic myeloid leukemia. Preferred PTK inhibitors for use in the invention are also those that specifically or non-specifically inhibit the activity of one or more PTKs selected from the group consisting of receptor tyrosine kinases for platelet-derived growth factor and stem cell factor (SCF), and c-Kit. The amount of the PTK used in conjunction with the vascular device is an amount sufficient to prevent or inhibit proliferation of vascular smooth muscle cells in an area within a blood vessel immediately adjacent to and/or proximal to the vascular device. In the preferred embodiment, the vascular device is coated with 4-{(4-methyl-1-piperazinyl)methyl}-N-{4-methyl-3-{{4-(3-pyrimidinyl}amino}-phenyl}benzamide and/or a pharmaceutically-suitable salt thereof (preferably the methane sulphonate salt).

A second embodiment of the invention is directed to a corresponding method for specifically preventing or inhibiting proliferation of VSMCs. Here, the method comprises coating, adsorbing, impregnating, or covalently or ionically bonding to the vascular device an amount of a PTK inhibitor; the amount being sufficient to prevent or inhibit proliferation of

VSMCs in an area within a blood vessel immediately adjacent to and/or proximal to the vascular device when the device is deployed within the lumen of a blood vessel. The preferred PTK inhibitor is 4-{(4-methyl-1-piperazinyl)methyl}-N-{4-methyl-3-{{4-(3-pyrimidinyl}amino}-phenyl}benzamide and/or a pharmaceutically-suitable salt thereof.

A third embodiment of the invention is directed to a systemic method of preventing or inhibiting restenosis of blood vessels following vascular intervention. The method comprises systemically administering an amount of a PTK inhibitor (preferably orally), the amount administered being sufficient to prevent or inhibit proliferation of VSMCs in an area within a blood vessel immediately adjacent to and/or proximal to the area where the vascular intervention took place. Again, the preferred PTK inhibitor for use in this embodiment of the invention is 4-{(4-methyl-1-piperazinyl)methyl}-N-{4-methyl-3-{{4-(3-pyrimidinyl}amino}-phenyl}benzamide and/or a pharmaceutically-suitable salt thereof.

Compounds For Use In The Invention:

Any compound now known or discovered in the future that inhibits the action of PTKs can be used in the subject invention. Specific compounds whose anti-PTK activity has been documented, and thus can be used in the present invention, include (without limitation): pyridopyrimidines, phtalimides, chinolines, chinazolines, flavonoides, and benzothiazoles.

Among the most extensively studied PTK inhibitors are the tyrophostins and quinazoline derivatives. These compounds are currently under investigation as potential anti-cancer drugs. For example, tyrophostins and quinazoline have been shown to synergize with antibodies to EGFR and to established anti-cancer drugs like cisplatin to inhibit the growth of squamous cell carcinoma *in vivo* and to block the growth of human cancer cells over expressing HER2-ErbB2 (respectively). Tyrophostins are based on the benzylidenemalonitrile structure. Slight permutations in this structure have provided a range of potent inhibitors that selectively target EGFR, ErB-2 and v-Abl. Thus tyrophostins can be used alone or in combination with other PTK inhibitors to suppress VSMC proliferation into the lumen of blood vessels.

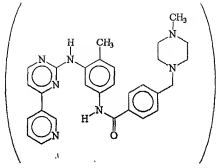
The quinazoline family of compounds includes the brominated quinazoline derivative, an early EGFR inhibitor that was found to be more than 3-fold more potent than any other

tyrosine kinase inhibitor yet described (with an IC_{50} of 29 pM). In addition, it has little affinity for PDGFR, FGFR, insulin receptor, the CSF receptor and Src, even at micromolar concentrations. Because of this extraordinary inhibitory activity and specificity, the quinazoline derivatives are a major focus of research aimed at developing kinase inhibitors as anti-cancer agents. Thus, these compounds can also be used in the present invention, either alone or in combination with other PTK inhibitors.

Another group of PTK inhibitory compounds, dianilinopthalimides, were rationally designed from the natural product PTK inhibitor staurosporine aglycon (see Appendix C). These compounds have been shown to be competitive inhibitors of ATP and to date more than 250 dianilinpthalimide derivatives have been synthesized and evaluated for their biological activity. The derivative CGP5211 has displayed a good amount of specificity towards EGFR (IC_{50}=3mM), but also shows some inhibitory activity towards PKC. This observation led to the design of CGP53353 derivative, which showed lower specificity towards PKC isozymes. Thus, dianilinopthalimides can also be used as a PTK inhibitor in the present invention.

A large number of other compounds are known to be PTK inhibitors. These compounds, all of which can be used in the present invention, include bryostatins, defensins, genistein, H8, herbimycin A, tyrophostins, K-252a, lavendustin A, phorbol esters, staurosporines, and suramin.

The preferred PTK inhibitor for use in the present invention is 4-{(4-methyl-1-piperazinyl)methyl}-N-{4-methyl-3-{{4-(3-pyrimidinyl}amino}-phenyl}benzamide and pharmaceutically-suitable salts thereof (preferably the mesyl salt):



This compound, originally designated STI-571, is marketed commercially in the United States by Novartis under the trademark "Glivec." It is approved by the U.S. Food and Drug Administration for the treatment of chronic myeloid leukemia. See EP 0 564 409 A and WO 99/03854.

Modes of Administration:

One embodiment of the invention is a method of preventing restenosis of blood vessels following a vascular injury or intervention by systemically administering one or more PTK inhibitors. The preferred route is orally. The PTK inhibitor may also be administered intravenously, intra-arterially, intramuscularly, percutaneously, parenterally, or rectally.

Specifically, systemic or topical administration is accomplished via a pharmaceutical composition comprising an active compound, *i.e.*, a PTK inhibitor or a pharmaceutically-acceptable salt thereof, in combination with an acceptable carrier therefor and optionally in combination with other therapeutically-active ingredients or inactive accessory ingredients. The carrier must be pharmaceutically-acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient. Suitable pharmaceutical compositions include those suitable for oral, topical (i.e. intra-lumen), rectal or parenteral (including subcutaneous, intramuscular and intravenous) administration.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. The term "unit dosage" or "unit dose" is denoted to mean a predetermined amount of the active ingredient sufficient to be effective for treating an indicated activity or condition. Making each type of pharmaceutical composition includes the step of bringing the active compound into association with a carrier and one or more optional accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound into association with a liquid or solid carrier and then, if necessary, shaping the product into the desired unit dosage form.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, boluses or lozenges, each containing a predetermined amount of the active compound; as a powder or granules; or in liquid form, *e.g.*, as an aqueous solution, suspension, syrup, elixir, emulsion, dispersion, or the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free-flowing form, *e.g.*, a powder or granules, optionally mixed with accessory ingredients, *e.g.*, binders, lubricants, inert diluents, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active compound with any suitable carrier.

Formulations suitable for parenteral administration conveniently comprise a sterile preparation of the active compound in, for example, water for injection, saline, a polyethylene glycol solution and the like, which is preferably isotonic with the blood of the recipient.

Useful formulations also comprise concentrated solutions or solids containing the PTK-inhibitory compound, which upon dilution with an appropriate solvent give a solution suitable for parenteral administration.

Preparations for topical or local applications comprise aerosol sprays, lotions, gels, ointments, suppositories etc., and pharmaceutically-acceptable vehicles therefore such as water, saline, lower aliphatic alcohols, polyglycerols such as glycerol, polyethylene glycerol,

esters of fatty acids, oils and fats, silicones, and other conventional topical carriers. In topical formulations, the PTK inhibitors are preferably utilized at a concentration of from about 0.1% to 5.0% by weight.

Compositions suitable for rectal administration, comprise a suppository, preferably bullet-shaped, containing the active ingredient and pharmaceutically-acceptable vehicles therefore such as hard fat, hydrogenated cocoglyceride, polyethylene glycol and the like. In suppository formulations, the PTK inhibitors are preferably utilized at concentrations of from about 0.1% to 10% by weight.

Compositions suitable for rectal administration may also comprise a rectal enema unit containing the active ingredient and pharmaceutically-acceptable vehicles therefore such as 50% aqueous ethanol or an aqueous salt solution which is physiologically compatible with the rectum or colon. The rectal enema unit consists of an applicator tip protected by an inert cover, preferably comprised of polyethylene, lubricated with a lubricant such as white petrolatum and preferably protected by a one-way valve to prevent back-flow of the dispensed formula, and of sufficient length, preferably two inches, to be inserted into the colon via the anus. In rectal formulations, the PTK inhibitors are preferably utilized at concentrations of from about 5.0-10% by weight.

Useful formulations also comprise concentrated solutions or solids containing the active ingredient which upon dilution with an appropriate solvent, preferably saline, give a solution suitable for rectal administration. The rectal compositions include aqueous and non-aqueous formulations which may contain conventional adjuvants such as buffers, bacteriostats, sugars, thickening agents and the like. The compositions may be presented in rectal single dose or multi-dose containers, for example, rectal enema units.

Preparations for topical or local surgical applications for treating a blood vessel within its lumen comprise swabs or catheters suitable for such purposes. In both topical or local surgical applications, the sterile preparations of PTK inhibitor are preferably utilized at concentrations of from about 0.1% to 5.0% by weight applied to a dressing.

Compositions suitable for administration by inhalation include formulations wherein the active ingredient is a solid or liquid admixed in a micronized powder having a particle size in the range of about 5 microns or less to about 500 microns or liquid formulations in a

suitable diluent. These formulations are designed for rapid inhalation through the oral passage from a conventional delivery systems such as inhalers, metered-dose inhalers, nebulizers, and the like. Suitable liquid nasal compositions include conventional nasal sprays, nasal drops and the like, of aqueous solutions of the active ingredient(s).

In addition to the aforementioned ingredients, the formulations of this invention may further include one or more optional accessory ingredient(s) utilized in the art of pharmaceutical formulations, i.e., diluents, buffers, flavoring agents, colorants, binders, surface active agents, thickeners, lubricants, suspending agents, preservatives (including antioxidants) and the like.

The amount of the PTK inhibitor required to be effective for inhibiting VSMC proliferation will, of course, vary with the individual mammal being treated and is ultimately at the discretion of the medical or veterinary practitioner. The factors to be considered include the condition being treated, the route of administration, the nature of the formulation, the mammal's body weight, surface area, age and general condition, and the particular PTK inhibitor to be administered. In general, a suitable effective dose is in the range of about 0.01 to about 500 mg/kg body weight per day of the selected PTK inhibitor. The total daily dose may be given as a single dose, multiple doses, *e.g.*, two to six times per day, or by intravenous infusion for a selected duration. Dosages above or below the range cited above are within the scope of the present invention and may be administered to the individual patient if desired and necessary.

The PTK inhibitors may be administered prophylactically (in the preferred embodiment immediately post-surgery), chronically, or acutely.

Specifically addressing the preferred embodiment, Novartis sells STI-571 in capsules that provide the equivalent of 100 mg of the free base form of STI-571. When administered orally (the preferred route), the preferred amount of STI-571 for use in the present invention is from 100 to 800 mg daily, taken in from one to four equal doses. Considerably larger doses, up to 1,200 mg/m^2/day, may also be given. Doses above 1,200 mg/m^2/day are not recommended.

The methods of the present invention include the administration, by local delivery to a site of injury, of compounds that have the ability to inhibit PTK activity. Non-limiting examples of local delivery systems for use in the present invention include intravascular drug delivery catheters, wires, pharmacological stents and endoluminal paving.

In the preferred embodiment using local delivery, the compounds for use in the present invention are administered to the site of recanalization by direct intravascular deposition using intravascular catheters. Catheter systems for use in the present invention, include, for example, pressure-driven catheters, diffusion catheters and mechanical catheters. Pressure-driven catheter systems that can be used in the present invention include porous catheters; microporous catheters, for example, those made by Cordis Corporation; macroporous catheters; transport catheters, for example, those made by Cardiovascular Dynamics/Boston Scientific; channeled balloon catheters, for example, those made by Boston Scientific; and infusion sleeve catheters, for example, those made by LocalMed. See, for example, U.S. Pat. No. 5,279,565.

The PTK inhibitors may also be administered locally via diffusion-based catheter systems, including for example, double balloon, dispatch, hydrogel and coated stent catheters. The methods of the invention also include local administration of the compounds used in the methods of the present invention by mechanical device-based catheter systems, such as iontophoretic balloon catheters.

The compounds for use in the present invention may be administered by local delivery at a time proximal to the recanalization procedure or at a time after the recanalization procedure. The compounds for use in the invention may be delivered in a single dose or delivered in repeat doses.

The ability to deliver the PTK inhibitory compounds used in the present invention may be evaluated *in vivo* using known animal models, including the porcine coronary model described in the Examples. Thus, for example, a PTK inhibitor to be used in the methods of the present invention is administered by local delivery to a porcine at a site of vascular injury. The porcine is sacrificed and then examined by known cytological, histological, and other methods, including, for example, fluorescence microscopy.

Optimum conditions for delivery of the PTK inhibitory compounds for use in the methods of the invention may vary with the different local delivery systems used, as well as the properties and concentrations of the compounds used. Conditions may be optimized for inhibition of VSMC proliferation at the site of injury such that significant arterial blockage due to restenosis does not occur, as measured, for example, by the proliferative ability of the VSMCs, or by changes in the vascular resistance or lumen diameter. Conditions which may be optimized include, for example, the concentrations of the compounds, the delivery volume, the delivery rate, the depth of penetration of the vessel wall, the proximal inflation pressure, the amount and size of perforations and the fit of the drug delivery catheter balloon.

In a particularly preferred route of administration, the PTK inhibitory compound is coated or adsorbed onto a vascular stent, a prosthetic venous/arterial graft, or an autologous vascular graft. Alternatively, the PTK inhibitor may be impregnated therein, or covalently or ionically bonded thereto.

The preferred application of the PTK inhibitor to the stent, graft, or prosthesis is by conventional methods which are known in the art. These methods include, without limitation, dipping, steeping and spraying the article with the PTK inhibitor. Additional coating and impregnation techniques using pressure to force the coating into the substrate interstices are also contemplated. Multiple layers of the bio-active coating may be applied to the article. The stent, graft or prosthesis may first be coated with a polymeric coating to provide sustained release of the PTK inhibitor over a period of days, week, or months. Preferably, from about 1 to about 10 layers of the PTK inhibitory agent are applied to the surface of the stent, graft, or prosthesis.

Devices and Autologous Grafts According to the Invention:

As noted in the previous paragraph, one preferred route to administer the PTK inhibitory compounds is to adhere them onto a stent, autologous graft, or vascular prosthesis. In the present invention, any such vascular medical device may be used, including catheters, stents, sheets, tubes, balloons, and the like. The term "medical device" as used herein shall generically designate all such vascular medical devices, whether synthetic, semi-synthetic, or autologous tissue or material.

Preferably the medical device of the present invention is an implantable device such as a vascular graft, endoprosthesis or stent, that has been treated, coated, or otherwise manipulated to have coated on at least one surface a compound that inhibits PTK activity. For purposes of this invention, the term "vascular graft" is meant to include all endoprostheses which are generally introduced via catheter. In the preferred embodiment, the medical device is coated with STI-571. Other medical devices may also be coated, such as catheters which are minimally invasive. The vascular graft may include a hollow tubular body having an inner and an outer hydrophobic surface, the outer surface or both surfaces of which are coated with the PTK inhibitory compound.

Most preferably, the device of the present invention is a small caliber vascular stent or graft, made of metal or polymeric material (such as poly(tetrafluoroethylene)). This includes stents made of polymeric materials and coated with distinct materials, such as the polytetrafluoroethylene stent described in U.S. Pat. No. 6,306,165.

Vascular stents, the preferred medical device of the subject invention, are miniature mesh tubes that are implanted in the arteries to keep blocked portions open after angioplasty procedures. Working as scaffolding for the treated artery, stents are flexible yet quite strong, are generally easy (for a skilled physician) to deliver via catheter, and are readily seen on a fluoroscope. Stents are pre-mounted on balloon catheters which are used to deliver the stent to the treatment site and then expand the stent into place after the blockage is cleared.

Any stent now known or developed in the future can be coated with a PTK inhibitor according to the present invention. Perhaps the largest commercial supplier of vascular stents is Medtronic, 710 Medtronic Parkway, Minneapolis, Minnesota. Medtronic also has facilities located in Tolochenaz, Switzerland; Ontario, Canada; Causeway Bay, Hong Kong; and Gladesville, NSW, Australia. All of Medtronics stents, catheters, balloons, guide catheters, guidewires, and the like can be used in the present invention. Currently, Medtronic markets a very wide range of stents and other vascular medical devices under the "Discrete Technology," "S7," "S670," "S660," and "BeStent" trademarks.

Vascular stents are available from non-US-based manufacterers as well. For example, Biocompatibles Cardiovascular, of Farnham, United Kingdom, manufactures and sells a range of cardiovascular stents under the trademark "BiodivYsio."

The PTK inhibitor can be adhered or coated onto the medical device, or it can be chemically bonded, either covalently or ionically to the medical device. The PTK inhibitor may be bonded directly to the medical device, or bonded via a spacer group or linker. For covalent attachment, it is preferred that a polymeric medical device, or a polymer-coated medical device be used and that the PTK inhibitor be covalently bonded to the medical device via a spacer group or linker having a chain length of from 1 to 250 atoms. For example, the spacer group may include an alkyls, alkylamines, oxygenated polyolefins, aliphatic polyesters, polyamino acids, polyamines, hydrophilic polysiloxanes, hydrophilic polysilazanes, hydrophilic acrylates, hydrophilic methacrylates, linear and lightly branched polysaccharides, and the like.

In yet another embodiment of the invention, there is provided a surface-modified implantable sheet material whose treated surface when exposed to the intimal layer of a blood vessel exhibits anti-VSMC proliferation activity over extended periods of time. This implantable sheet material includes a hydrophobic substrate material having adhered or bonded thereto a compound that inhibits PTK activity, the preferred compound being STI-571. The sheet can be formed into surgical mesh patches or tubes to repair vascular defects and injuries.

EXAMPLES

The following Examples are included solely to provide a more thorough disclosure of the invention claimed herein. The Examples do not limit the invention in any fashion.

Example 1 - Vascular Smooth Muscle Cell Proliferation:

Porcine coronary VSMCs were grown to subconfluence in 96-well plates with DME media containing 10% FBS at 37°C for 3 to 5 days. After synchronization in serum-free DME media for 48 hours, the cells were stimulated with PDGF (20 ng/mL) for 24 hours, in the presence of STI-571 (0.01 to 10 M). BrdU was added to the wells for the last 5 hours of the stimulation period. The cells were subsequently dried for 24 hours at 60°C, fixed and denatured, and BrdU incorporation was determined using a colorimetric assay (ELISA) sold commercially by Roche Molecular Biochemicals (catalog no. 1,647,229), following the

manufacturer's protocol. See "Cell Proliferation ELISA, BrdU (Colorimetric) Instruction Manual," Version 3, September 2000, available from Roche Molecular Biochemicals. Briefly, the BrdU ELISA is a colorimetric immunoassay for quantification of cell proliferation. It is based on the measurement of BrdU incorporation during DNA synthesis. The colorimetric approach is a non-radioactive alternative to the equivalent ^{3}H-thymidine incorporation assay. See also Example 4.

The results of this Example are presented graphically in Fig. 1. DNA synthesis was assayed by incorporation of BrdU (in the same fashion as described in Example 4) after stimulation of the cells with platelet-derived growth factor (PDGF-ββ, 20 ng/ml) for 48 in the presence or absence (positive control) of STI-571. Each data point represents 5 to 7 wells, and is expressed as he mean +/- the standard deviation.

As can be seen from the figure, administration of STI-571 inhibited the proliferation of VSMCs in a dose-dependent fashion. This Example demonstrates the utility of the present invention to inhibit the proliferation of VSMCs.

Example 2 - Vascular Endothelial Cell Proliferation:

Porcine aortic vascular endothelial cells were grown to subconfluence in 96-well plates with DME media containing 10% FBS at 37°C for 3 to 5 days. After synchronization in serum-free DME media for 48 hours, the cells were stimulated with VEGF (20 ng/mL) for 24 hours, in the presence of STI-571 (0.01 to 10 M). BrdU was added to the wells for the last 5 hours of the stimulation period. The cells were subsequently dried for 24 hours at 60°C, fixed and denatured, and BrdU incorporation determined using the Roche ELISA described in Example 1.

The results of this Example are presented graphically in Fig. 2. As can be seen from this figure, STI-571 had a very minimal inhibitory effect on the proliferation of aortic vascular endothelial cells.

Taken in conjunction with the results of Example 1, this Example demonstrates the utility of the present invention to inhibit the proliferation of VSMCs selectively, while not having an appreciable inhibitory affect on the proliferation of aortic vascular endothelial cells.

Example 3 - Inhibition of Proliferation of Human Coronary Artery Vascular Smooth Muscle Cells by Increasing Concentrations of STI-571:

This Example demonstrates that human coronary artery vascular smooth muscle cells are inhibited in a dose-dependent fashion by STI-571.

Cyropreserved human coronary artery vascular smooth muscle cells (CC-2583) were purchased commercially from Clonetics (now a wholly-owned subsidiary of Cambrex Bio Science Walkersville, Inc., Walkersville, Maryland).

The cells were grown in canted-neck, filtered-cap, 25cm^2 culture flasks, at an initial seed density of 2500 cells per cm^2. The cells were grown in "SmGM-2"-brand smooth muscle growth medium (Cambrex, used as delivered from the manufacturer) plus 10% FBS in a humidified 37 °C, 5% CO_2 incubator. Media were changed initially after 24 hours, and then every 48 hrs subsequently. The cells were passed at approximately 80% confluency (~ 4-6 days). The proliferation assays were performed in 24-well culture plates.

On day 5, growth media were replaced with test media (growth media + STI-571), growth media (positive control, media + FBS), and serum-free media (negative control, the "SmGM-2"-brand media without any added FBS).

Cells were counted manually trypsinizing the cells on day 7, with each condition (3 wells) pooled into one micro-centrifuge tube. The cells were spun at 1.5 X g for 10 min. and then resuspended in 60 µl trypsin-neutralizing solution. The cells were then counted on a hemacytometer in quadruplicate.

The results are shown in Fig. 3. In the figure, cells were counted after being stimulated with 10% FBS for 48 hours. The data for each experiment was normalized to positive control wells containing FBS and no STI-571. Each point represents 18 to 21 wells from eight separate experiments. The center of each data point is the mean at each concentration of STI-571, and the error bars are the standard deviation at each concentration level.

The significance of this graph is that it clearly indicates that STI-571 inhibits, in a dose-dependent fashion, the proliferation of human coronary artery vascular smooth muscle cells. Because these cells are responsible for restenosis, this graph demonstrates the effectiveness of the present invention for inhibiting such restenosis.

Example 4 - Inhibition of DNA Synthesis in Human Coronary Artery Vascular Smooth Muscle Cells by STI-571:

This example demonstrates that STI-571 inhibits DNA synthesis in human coronary artery vascular smooth muscle cells.

The same cells as described in Example 3 were used. Culture conditions and exposure to the various test concentrations of STI-571 were also the same as in Example 3.

DNA incorporation was measured using a commercially-available BrdU assay (Roche Molecular Biochemicals, catalog no. 1,647,229). The BrDu labeling solution was added on day 6, and the cells then allowed to incubate for another 24 hrs (through day 7). The label solution was then removed and the cells were dried at 60 °C for one hour. The cells were then fixed using "FixDenat" fixing solution for one hour at room temperature. The fixing solution was then removed and anti-BrdU antibody solution added to the cells. The cells were then incubated for 2 hr at 37 °C.

The antibody solution was then removed substrate added to the wells. The plates were incubated at room temperature until sufficient color development occurred. The reactions were stopped by adding 1 M H_2SO_4 to the wells. The absorbance was then measured at 450nm (reference, 690 nm).

The results are shown in Fig. 4. Each data point represents 14 to 28 wells from two separate experiments, and are expressed as the means +/- the standard deviations. The significance of this Example is that it shows that STI-571 inhibits DNA synthesis in human coronary artery vascular smooth muscle cells. As in the previous Example, this is notable because these types of cells cause restenosis of stented vessels. By inhibiting the growth of such cells, restenosis is inhibited.

Example 5 - Inhibition of Migration of Human Coronary Artery Vascular Smooth Muscle Cells by STI-571:

This Example was performed to determine if STI-571 has any effect on the migration of human coronary vascular smooth muscle cells.

The cells described in Example 3 were used. The initial seed density was 4000 cells per filter (0.3 cm^2) in test media with 1% BSA and 20 ng/ml PDGF-ββ. The cells were then incubated in a humidified environment at 37 °C, 5% CO_2 for 24 hrs. The cells on the top side of the filter were then scraped away. The cells on bottom side of the filters were then fixed with ice-cold methanol for 10 min. The filters were rinsed with PBS and then stained with HarrisÆ Hematoxylin stain for 5 min. and again rinsed with PBS.

The cells were then counted manually under high-power magnification (400X) in quadruplicate.

The results are shown in Fig. 5. Data bars represent 6 membranes, and the data are presented as means normalized to control membranes (no STI-571) +/- standard deviations.

The significance of this Example is that it demonstrates that STI-571 inhibits the migration of human coronary vascular smooth muscle cells in a dose-dependent fashion. Because migration of these cells is a major contributor to restenosis after deployment of a stent, this Example demonstrates that the present invention can be used to inhibit this migration and hence inhibit restenosis.

Example 6 - Lack of Inhibitory Effect of STI-571 on Proliferation of Human Coronary Artery Endothelial Cells:

This Example demonstrates that the growth of human coronary artery endothelial cells are not inhibited in any fashion by STI-571.

Cyropreserved human coronary artery endothelial cells were purchased commercially from Clonetics (now a wholly-owned subsidiary of Cambrex Bio Science Walkersville, Inc., Walkersville, Maryland).

The cells were grown in canted-neck, filtered-cap, 25cm^2 culture flasks, at an initial seed density of 2500 cells per cm^2. The cells were grown in "EGM-MV"-brand smooth muscle growth medium (Cambrex, used as delivered from the manufacturer) plus 10% FBS in a humidified 37 °C, 5% CO_2 incubator. Media were changed initially after 24 hours, and then every 48 hrs subsequently. The cells were passed at approximately 80% confluency (~ 4-6 days). The proliferation assays were performed in 24-well culture plates.

On day 5, growth media were replaced with test media (growth media + STI-571), growth media (positive control, media + FBS), and serum-free media (negative control, the "EGM-MV"-brand media without any added FBS).

Cells were counted manually trypsinizing the cells on day 7, with each condition (3 wells) pooled into one micro-centrifuge tube. The cells were spun at 1.5 X g for 10 min. and then resuspended in 60 µl trypsin-neutralizing solution. The cells were then counted on a hemacytometer in quadruplicate.

The results are shown in Fig. 6. As can be seen from the figure, STI-571 did not have a significant effect on the proliferation of human coronary artery endothelial cells at any of the STI-571 concentrations tested. This Example, in conjunction with Examples 3-5, are significant because they show that STI-571 has a profound inhibitory effect on human vascular smooth muscle cells (inhibits proliferation, DNA replication, and cell migration), but does not inhibit the proliferation of endothelial cells. This is notable because the proliferation of endothelial cells around an inserted vascular stent is desirable so that the stent becomes firmly implanted within the vessel wall.

CLAIMS

What is claimed is:

1. A device for stenting a blood vessel, the device comprising:

a cardiovascular stent, autologous venous/arterial graft, prosthetic venous/arterial graft, vascular catheter, or vascular shunt having coated thereon, adsorbed thereto, impregnated therein, or covalently or ionically bonded thereto an amount of a protein tyrosine kinase inhibitor; the amount being sufficient to prevent or inhibit proliferation of vascular smooth muscle cells in an area within a blood vessel immediately adjacent to and/or proximal to the cardiovascular stent, autologous venous/arterial graft, prosthetic venous/arterial graft, vascular catheter or vascular shunt, while simultaneously not inhibiting the proliferation of vascular intimal cells.

2. The device of Claim 1, comprising a cardiovascular stent,

3. The device of Claim 1, comprising an autologous venous/arterial graft.

4. The device of Claim 1, comprising a prosthetic venous/arterial graft.

5. The device of Claim 1, comprising a vascular catheter.

6. The device of Claim 1, comprising a vascular shunt.

7. The device of Claim 1, wherein the protein tyrosine kinase inhibitor is a platelet-derived growth factor inhibitor.

8. The device of Claim 7, wherein the protein tyrosine kinase inhibitor is also a Bcr-Abl tyrosine kinase inhibitor.

9. The device of Claim 1, wherein the protein tyrosine kinase inhibitor is STI-571.

10. The device of Claim 1, wherein the protein tyrosine kinase inhibitor is 4-{(4-methyl-1-piperazinyl)methyl}-N-{4-methyl-3-{{4-(3-pyrimidinyl}amino}-phenyl}benzamide and/or a pharmaceutically-suitable salt thereof, the amount being sufficient to prevent or inhibit proliferation of vascular smooth muscle cells in an area within a blood vessel immediately adjacent to and/or proximal to the cardiovascular stent, autologous venous/arterial graft, prosthetic venous/arterial graft, vascular catheter or vascular shunt.

11. A device for stenting a blood vessel, the device comprising:

a cardiovascular stent, autologous venous/arterial graft, prosthetic venous/arterial graft, vascular catheter, or vascular shunt having coated thereon, adsorbed thereto, impregnated therein, or covalently or ionically bonded thereto an amount of 4-{(4-methyl-1-piperazinyl)methyl}-N-{4-methyl-3-{{4-(3-pyrimidinyl}amino}-phenyl}benzamide and/or a pharmaceutically-suitable salt thereof, the amount being sufficient to prevent or inhibit proliferation of vascular smooth muscle cells in an area within a blood vessel immediately adjacent to and/or proximal to the cardiovascular stent, autologous venous/arterial graft, prosthetic venous/arterial graft, vascular catheter or vascular shunt, while simultaneously not inhibiting the proliferation of vascular intimal cells.

12. The device of Claim 11, comprising a cardiovascular stent,

13. The device of Claim 11, comprising an autologous venous/arterial graft.

14. The device of Claim 11, comprising a prosthetic venous/arterial graft.

15. The device of Claim 11, comprising a vascular catheter.

16. The device of Claim 11, comprising a vascular shunt.

17. A method of preventing restenosis following vascular intervention, the method comprising coating, adsorbing, impregnating, or covalently or ionically bonding to a cardiovascular stent, autologous venous/arterial graft, prosthetic venous/arterial graft, vascular catheter or vascular shunt used in the vascular intervention an amount of a protein tyrosine kinase inhibitor; the amount being sufficient to prevent or inhibit proliferation of vascular smooth muscle cells in an area within a blood vessel immediately adjacent to and/or proximal to the cardiovascular stent, autologous venous/arterial graft, prosthetic venous/arterial graft, vascular catheter or vascular shunt, while simultaneously not inhibiting the proliferation of vascular intimal cells.

18. The method of Claim 17, wherein the cardiovascular stent, autologous venous/arterial graft, prosthetic venous/arterial graft, vascular catheter or vascular shunt is coated with a platelet-derived growth factor inhibitor.

19. The method of Claim 17, wherein the cardiovascular stent, autologous venous/arterial graft, prosthetic venous/arterial graft, vascular catheter or vascular shunt is coated with a Bcr-Abl tyrosine kinase inhibitor.

20. The device of Claim 17, wherein the cardiovascular stent, autologous venous/arterial graft, prosthetic venous/arterial graft, vascular catheter or vascular shunt is coated with STI-571.

21. The device of Claim 17, wherein the cardiovascular stent, autologous venous/arterial graft, prosthetic venous/arterial graft, vascular catheter or vascular shunt is coated with 4-{(4-methyl-1-piperazinyl)methyl}-N-{4-methyl-3-{{4-(3-pyrimidinyl}amino}-phenyl}benzamide and/or a pharmaceutically-suitable salt thereof.

22. A method of preventing restenosis following vascular intervention, the method comprising coating, adsorbing, impregnating, or covalently or ionically bonding to a cardiovascular stent, autologous venous/arterial graft, prosthetic venous/arterial graft, vascular catheter or vascular shunt used in the vascular intervention an amount of 4-{(4-methyl-1-piperazinyl)methyl}-N-{4-methyl-3-{{4-(3-pyrimidinyl}amino}-phenyl}benzamide and/or a pharmaceutically-suitable salt thereof, the amount being sufficient to prevent or inhibit proliferation of vascular smooth muscle cells in an area within a blood vessel immediately adjacent to and/or proximal to the cardiovascular stent, autologous venous/arterial graft, prosthetic venous/arterial graft, vascular catheter or vascular shunt, while simultaneously not inhibiting the proliferation of vascular intimal cells.

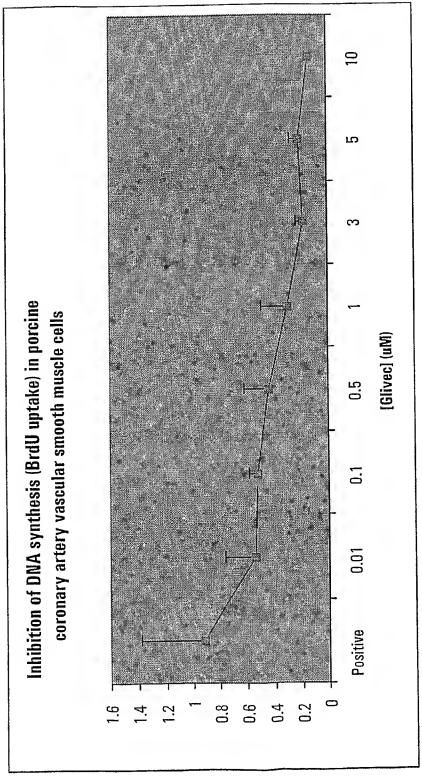

Inhibition of DNA synthesis (BrdU uptake) in porcine coronary artery vascular smooth muscle cells
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Positive
0.01
0.1
0.5
1
3
5
10
[Glivec] (uM)

FIG. 1

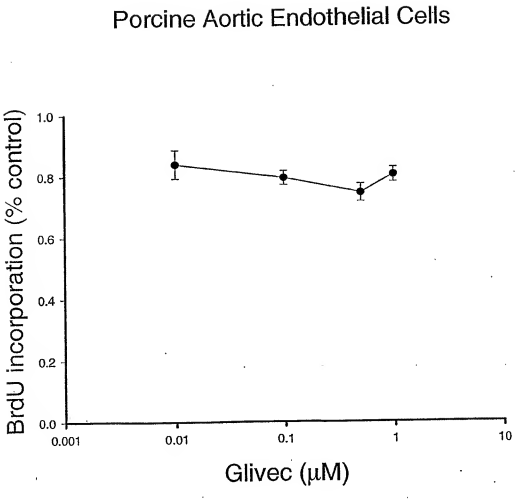

Porcine Aortic Endothelial Cells
BrdU incorporation (% control)
1.0
0.8
0.6
0.4
0.2
0.0
0.001
0.01
0.1
1
10
Glivec (μM)

FIG. 2

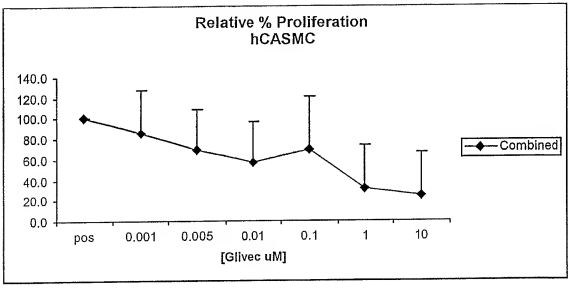

Relative % Proliferation
hCASMC
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
pos
0.001
0.005
0.01
0.1
1
10
[Glivec uM]
Combined

FIG. 3

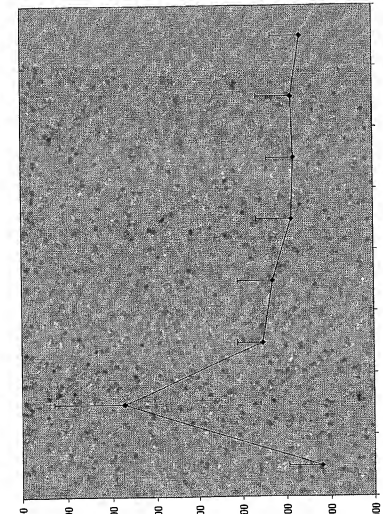

Inhibition of DNA Synthesis in HCAVSMC by Glivec
Corrected Absorbance (450-690)
0.800
0.700
0.600
0.500
0.400
0.300
0.200
0.100
0.000
Negative
Positive
0.001
0.005
0.01
0.1
1
10
[Glivec] (uM)

FIG. 4

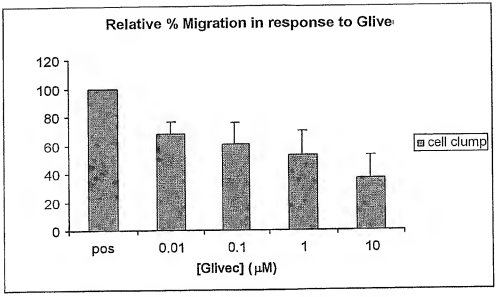

Relative % Migration in response to Glive
120
100
80
60
40
20
0
pos
0.01
0.1
1
10
[Glivec] (μM)
cell clump

FIG. 5

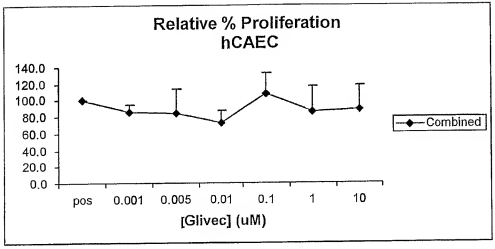

Relative % Proliferation
hCAEC
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
pos
0.001
0.005
0.01
0.1
1
10
[Glivec] (uM)
Combined

FIG. 6

'ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND SEQUENCE LISTING

<110> Wolff, Matthew R.

<120> VASCULAR STENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN

<130> 09820.189

<150> 60/343,732
<151> 2001-10-25

<160> 25

<170> PatentIn version 3.1

<210> 1
<211> 3000
<212> DNA
<213> Homo sapiens

<400> 1
atggggccgg ccccgctgcc gctgctgctg ggcctcttcc tccccgcgct ctggcgtaga
60

gctatcactg aggcaaggga agaagccaag ccttacccgc tattcccggg acctttttcca 1
20

gggagcctgc aaactgacca cacaccgctg ttatcccttc ctcacgccag tgggtaccag 1
80

cctgccttga tgttttcacc aacccagcct ggaagaccac atacaggaaa cgtagccatt 2
40

ccccaggtga cctctgtcga atcaaagccc ctaccgcctc ttgccttcaa acacacagtt 3
00

ggacacataa tactttctga acataaaggt gtcaaattta attgctcaat caatgtacct 3
60

aatatatacc aggacaccac aatttcttgg tggaaagatg ggaaggaatt gcttggggga 4
20

catcatcgaa ttacacagtt ttatccagat gatgaagtta cagcaataat cgcttccttc 4
80

agcataacca gtgtgcagcg ttcagacaat gggtcgtata tctgtaagat gaaaataaac 5
40

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
aatgaagaga tcgtgtctga tcccatctac atcgaagtac aaggacttcc tcactttact 6
00

aagcagcctg agagcatgaa tgtcaccaga aacacagcct tcaacctcac ctgtcaggct 6
60

gtgggcccgc ctgagcccgt caacattttc tgggttcaaa acagtagccg tgttaacgaa 7
20

cagcctgaaa aatcccccgg cgtgctaact gttccaggcc tgacggagat ggcggtcttc 7
80

agttgtgagg cccacaatga caaagggctg accgtgtccc agggagtgca gatcaacatc 8
40

aaagcaattc cctccccacc aactgaagtc agcatccgta acagcactgc acacagcatt 9
00

ctgatctcct gggttcctgg ttttgatgga tactccccgt tcaggaattg cagcattcag 9
60

gtcaaggaag ctgatccgct gggtaatggc tcagtcatga tttttaacac ctctgcctta 10
20

ccacatctgt accaaatcaa gcagctgcaa gccctggcta attacagcat tggtgtttcc 10
80

tgcatgaatg aaataggctg gtctgcagtg agcccttgga ttctagcaag cacgactgaa 11
40

ggagccccat cagtagcacc tttaaatgtc actgtgtttc tgaatgaatc tagtgataat 12
00

gtggacatca gatggatgaa gcctccgact aagcagcagg atggagaact ggtgggctac 12
60

cggatatccc acgtgtggca gagtgcaggg atttccaaag agctcttgga ggaagttggc 13
20

cagaatggca gccgagctcg gatctctgtt caagtccaca atgctacgtg cacagtgagg 13
80

attgcagccg tcaccagagg gggagttggg cccttcagtg atccagtgaa aatatttatc 14
40

cctgcacacg gttgggtaga ttatgccccc tcttcaactc cggcgcctgg caacgcagat 15
00

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
cctgtgctca tcatctttgg ctgcttttgt ggatttattt tgattgggtt gattttatac 15
60

atctccttgg ccatcagaaa aagagtccag gagacaaagt ttgggaatgc attcacagag 16
20

gaggattctg aattagtggt gaattatata gcaaagaaat ccttctgtcg gcgagccatt 16
80

gaacttacct tacatagctt gggagtcagt gaggaactac aaaataaact agaagatgtt 17
40

gtgattgaca ggaatcttct aattcttgga aaaattctgg gtgaaggaga gtttgggtct 18
00

gtaatggaag gaaatcttaa gcaggaagat gggacctctc tgaaagtggc agtgaagacc 18
60

atgaagttgg acaactcttc acatcgggag atcgaggagt ttctcagtga ggcagcgtgc 19
20

atgaaagact tcagccaccc aaatgtcatt cgacttctag gtgtgtgtat agaaatgagc 19
80

tctcaaggca tcccaaagcc catggtaatt ttacccttca tgaaatacgg ggacctgcat 20
40

acttacttac tttattcccg attggagaca ggaccaaagc atattcctct gcagacacta 21
00

ttgaagttca tggtggatat tgccctggga atggagtatc tgagcaacag gaattttctt 21
60

catcgagatt tagctgctcg aaactgcatg ttgcgagatg acatgactgt ctgtgttgcg 22
20

gacttcggcc tctctaagaa gatttacagt ggcgattatt accgccaagg ccgcattgct 22
80

aagatgcctg ttaaatggat cgccatagaa agtcttgcag accgagtcta cacaagtaaa 23
40

agtgatgtgt gggcatttgg cgtgaccatg tgggaaatac gtacgcgggg aatgactccc 24
00

tatcctgggg tccagaacca tgagatgtat gactatcttc tccatggcca caggttgaag 24
60

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

cagcccgaag actgcctgga tgaactgtat gaaataatgt actcttgctg gagaaccgat 25
20

cccttagacc gccccacctt ttcagtattg aggctgcagc tagaaaaact cttagaaagt 25
80

ttgcctgacg ttcggaacca agcagacgtt atttacgtca atacacagtt gctggagagc 26
40

tctgagggcc tggcccaggg ccccaccctt gctccactgg acttgaacat cgaccctgac 27
00

tctataattg cctcctgcac tccccgcgct gccatcagtg tggtcacagc agaagttcat 27
60

gacagcaaac ctcatgaagg acggtacatc ctgaatgggg gcagtgagga atgggaagat 28
20

ctgacttctg ccccctctgc tgcagtcaca gctgaaaaga acagtgtttt accgggggag 28
80

agacttgtta ggaatggggt ctcctggtcc cattcgagca tgctgcccttt gggaagctca 29
40

ttgcccgatg aacttttgtt tgctgacgac tcctcagaag gctcagaagt cctgatgtga 30
00

<210> 2
<211> 1353
<212> DNA
<213> Homo sapiens

<400> 2
atgtcagcaa tacaggccgc ctggccatcc ggtacagaat gtattgccaa gtacaacttc
60

cacggcactg ccgagcagga cctgcccttc tgcaaaggag acgtgctcac cattgtggcc 1
20

gtcaccaagg accccaactg gtacaaagcc aaaaacaagg tgggccgtga gggcatcatc 1
80

ccagccaact acgtccagaa gcgggagggc gtgaaggcgg gtaccaaact cagcctcatg 2
40

ccttggttcc acggcaagat cacacgggag caggctgagc ggcttctgta cccgccggag 3
00

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

acaggcctgt tcctggtgcg ggagagcacc aactaccccg gagactacac gctgtgcgtg 3
60

agctgcgacg gcaaggtgga gcactaccgc atcatgtacc atgccagcaa gctcagcatc 4
20

gacgaggagg tgtactttga gaacctcatg cagctggtgg agcactacac ctcagacgca 4
80

gatggactct gtacgcgcct cattaaacca aaggtcatgg agggcacagt ggcggcccag 5
40

gatgagttct accgcagcgg ctgggccctg aacatgaagg agctgaagct gctgcagacc 6
00

atcgggaagg gggagttcgg agacgtgatg ctgggcgatt accgagggaa caaagtcgcc 6
60

gtcaagtgca ttaagaacga cgccactgcc caggccttcc tggctgaagc ctcagtcatg 7
20

acgcaactgc ggcatagcaa cctggtgcag ctcctgggcg tgatcgtgga ggagaagggc 7
80

gggctctaca tcgtcactga gtacatggcc aaggggagcc ttgtggacta cctgcggtct 8
40

aggggtcggt cagtgctggg cggagactgt ctcctcaagt tctcgctaga tgtctgcgag 9
00

gccatggaat acctggaggg caacaatttc gtgcatcgag acctggctgc ccgcaatgtg 9
60

ctggtgtctg aggacaacgt ggccaaggtc agcgactttg gtctcaccaa ggaggcgtcc 10
20

agcacccagg acacgggcaa gctgccagtc aagtggacag cccctgaggc cctgagagag 10
80

aagaaattct ccactaagtc tgacgtgtgg agtttcggaa tccttctctg ggaaatctac 11
40

tcctttgggc gagtgcctta tccaagaatt cccctgaagg acgtcgtccc tcgggtggag 12
00

aagggctaca agatggatgc ccccgacggc tgcccgcccg cagtctatga agtcatgaag 12
60

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

aactgctggc acctggacgc cgccatgcgg ccctccttcc tacagctccg agagcagctt 13
20

gagcacatca aaacccacga gctgcacctg tga 13
53

<210> 3
<211> 3768
<212> DNA
<213> Homo sapiens

<400> 3
atggagctgg cggccttgtg ccgctggggg ctcctcctcg ccctcttgcc ccccggagcc
60

gcgagcaccc aagtgtgcac cggcacagac atgaagctgc ggctccctgc cagtcccgag 1
20

acccacctgg acatgctccg ccacctctac cagggctgcc aggtggtgca gggaaacctg 1
80

gaactcacct acctgcccac caatgccagc ctgtccttcc tgcaggatat ccaggaggtg 2
40

cagggctacg tgctcatcgc tcacaaccaa gtgaggcagg tcccactgca gaggctgcgg 3
00

attgtgcgag gcacccagct ctttgaggac aactatgccc tggccgtgct agacaatgga 3
60

gacccgctga acaataccac ccctgtcaca ggggcctccc caggaggcct gcgggagctg 4
20

cagcttcgaa gcctcacaga gatcttgaaa ggaggggtct tgatccagcg gaacccccag 4
80

ctctgctacc aggacacgat tttgtggaag gacatcttcc acaagaacaa ccagctggct 5
40

ctcacactga tagacaccaa ccgctctcgg gcctgccacc cctgttctcc gatgtgtaag 6
00

ggctcccgct gctgggagga gagttctgag gattgtcaga gcctgacgcg cactgtctgt 6
60

gccggtggct gtgcccgctg caaggggcca ctgcccactg actgctgcca tgagcagtgt 7

'ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
20

gctgccggct gcacgggccc caagcactct gactgcctgg cctgcctcca cttcaaccac 7
80

agtggcatct gtgagctgca ctgcccagcc ctggtcacct acaacacaga cacgtttgag 8
40

tccatgccca atcccgaggg ccggtataca ttcggcgcca gctgtgtgac tgcctgtccc 9
00

tacaactacc tttctacgga cgtgggatcc tgcaccctcg tctgccccct gcacaaccaa 9
60

gaggtgacag cagaggatgg aacacagcgg tgtgagaagt gcagcaagcc ctgtgcccga 10
20

gtgtgctatg gtctgggcat ggagcacttg cgagaggtga gggcagttac cagtgccaat 10
80

atccaggagt ttgctggctg caagaagatc tttgggagcc tggcatttct gccggagagc 11
40

tttgatgggg acccagcctc caacactgcc ccgctccagc cagagcagct ccaagtgttt 12
00

gagactctgg aagagatcac aggttaccta tacatctcag catggccgga cagcctgcct 12
60

gacctcagcg tcttccagaa cctgcaagta atccggggac gaattctgca caatggcgcc 13
20

tactcgctga ccctgcaagg gctgggcatc agctggctgg ggctgcgctc actgagggaa 13
80

ctgggcagtg gactggccct catccaccat aacacccacc tctgcttcgt gcacacggtg 14
40

ccctgggacc agctctttcg gaacccgcac caagctctgc tccacactgc caaccggcca 15
00

gaggacgagt gtgtgggcga gggcctggcc tgccaccagc tgtgcgcccg agggcactgc 15
60

tggggtccag ggcccaccca gtgtgtcaac tgcagccagt tccttcgggg ccaggagtgc 16
20

gtggaggaat gccgagtact gcaggggctc cccagggagt atgtgaatgc caggcactgt 16

'ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
80

ttgccgtgcc accctgagtg tcagccccag aatggctcag tgacctgttt tggaccggag 17
40

gctgaccagt gtgtggcctg tgcccactat aaggaccctc ccttctgcgt ggcccgctgc 18
00

cccagcggtg tgaaacctga cctctcctac atgcccatct ggaagtttcc agatgaggag 18
60

ggcgcatgcc agccttgccc catcaactgc acccactcct gtgtggacct ggatgacaag 19
20

ggctgccccg ccgagcagag agccagccct ctgacgtcca tcgtctctgc ggtggttggc 19
80

attctgctgg tcgtggtctt gggggtggtc tttgggatcc tcatcaagcg acggcagcag 20
40

aagatccgga agtacacgat gcggagactg ctgcaggaaa cggagctggt ggagccgctg 21
00

acacctagcg gagcgatgcc caaccaggcg cagatgcgga tcctgaaaga gacggagctg 21
60

aggaaggtga aggtgcttgg atctggcgct tttggcacag tctacaaggg catctggatc 22
20

cctgatgggg agaatgtgaa aattccagtg gccatcaaag tgttgaggga aaacacatcc 22
80

cccaaagcca acaaagaaat cttagacgaa gcatacgtga tggctggtgt gggctcccca 23
40

tatgtctccc gccttctggg catctgcctg acatccacgg tgcagctggt gacacagctt 24
00

atgccctatg gctgcctctt agaccatgtc cgggaaaacc gcggacgcct gggctcccag 24
60

gacctgctga actggtgtat gcagattgcc aaggggatga gctacctgga ggatgtgcgg 25
20

ctcgtacaca gggacttggc cgctcggaac gtgctggtca agagtcccaa ccatgtcaaa 25
80

attacagact tcgggctggc tcggctgctg gacattgacg agacagagta ccatgcagat 26

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
40

ggggggcaagg tgcccatcaa gtggatggcg ctggagtcca ttctccgccg gcggttcacc 27
00

caccagagtg atgtgtggag ttatggtgtg actgtgtggg agctgatgac ttttggggcc 27
60

aaaccttacg atgggatccc agcccgggag atccctgacc tgctggaaaa gggggagcgg 28
20

ctgccccagc ccccatctg caccattgat gtctacatga tcatggtcaa atgttggatg 28
80

attgactctg aatgtcggcc aagattccgg gagttggtgt ctgaattctc ccgcatggcc 29
40

agggaccccc agcgctttgt ggtcatccag aatgaggact tgggcccagc cagtcccttg 30
00

gacagcacct tctaccgctc actgctggag gacgatgaca tgggggacct ggtggatgct 30
60

gaggagtatc tggtacccca gcagggcttc ttctgtccag accctgcccc gggcgctggg 31
20

ggcatggtcc accacaggca ccgcagctca tctaccagga gtggcggtgg ggacctgaca 31
80

ctagggctgg agccctctga agaggaggcc cccaggtctc cactggcacc ctccgaaggg 32
40

gctggctccg atgtatttga tggtgacctg ggaatggggg cagccaaggg gctgcaaagc 33
00

ctccccacac atgaccccag ccctctacag cggtacagtg aggaccccac agtacccctg 33
60

ccctctgaga ctgatggcta cgttgccccc ctgacctgca gcccccagcc tgaatatgtg 34
20

aaccagccag atgttcggcc ccagcccctc tcgccccgag agggccctct gcctgctgcc 34
80

cgacctgctg gtgccactct ggaaagggcc aagactctct ccccagggaa gaatggggtc 35
40

gtcaaagacg tttttgcctt tgggggtgcc gtggagaacc ccgagtactt gacaccccag 36

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
00

ggaggagctg cccctcagcc ccaccctcct cctgccttca gcccagcctt cgacaacctc 36
60

tattactggg accaggaccc accagagcgg ggggctccac ccagcacctt caaagggaca 37
20

cctacggcag agaacccaga gtacctgggt ctggacgtgc cagtgtga 37
68

<210> 4
<211> 3429
<212> DNA
<213> Homo sapiens

<400> 4
atggctttct gtgctaaaat gaggagctcc aagaagactg aggtgaacct ggaggcccct
60

gagccagggg tggaagtgat cttctatctg tcggacaggg agcccctccg gctgggcagt 1
20

ggagagtaca cagcagagga actgtgcatc agggctgcac aggcatgccg tatctctcct 1
80

ctttgtcaca acctctttgc cctgtatgac gagaacacca agctctggta tgctccaaat 2
40

cgcaccatca ccgttgatga caagatgtcc ctccggctcc actaccggat gaggttctat 3
00

ttcaccaatt ggcatggaac caacgacaat gagcagtcag tgtggcgtca ttctccaaag 3
60

aagcagaaaa atggctacga gaaaaaaaag attccagatg caacccctct ccttgatgcc 4
20

agctcactgg agtatctgtt tgctcaggga cagtatgatt tggtgaaatg cctggctcct 4
80

attcgagacc ccaagaccga gcaggatgga catgatattg agaacgagtg tctagggatg 5
40

gctgtcctgg ccatctcaca ctatgccatg atgaagaaga tgcagttgcc agaactgccc 6
00

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
aaggacatca gctacaagcg atatattcca gaaacattga ataagtccat cagacagagg 6
60

aaccttctca ccaggatgcg gataaataat gttttcaagg atttcctaaa ggaatttaac 7
20

aacaagacca tttgtgacag cagcgtgtcc acgcatgacc tgaaggtgaa atacttggct 7
80

accttggaaa ctttgacaaa acattacggt gctgaaatat ttgagacttc catgttactg 8
40

atttcatcag aaaatgagat gaattggttt cattcgaatg acggtggaaa cgttctctac 9
00

tacgaagtga tggtgactgg gaatcttgga atccagtgga ggcataaacc aaatgttgtt 9
60

tctgttgaaa aggaaaaaaa taaactgaag cggaaaaaac tggaaaataa agacaagaag 10
20

gatgaggaga aaaacaagat ccgggaagag tggaacaatt tttcattctt ccctgaaatc 10
80

actcacattg taataaagga gtctgtggtc agcattaaca agcaggacaa caagaaaatg 11
40

gaactgaagc tctcttccca cgaggaggcc ttgtcctttg tgtccctggt agatggctac 12
00

ttccggctca cagcagatgc ccatcattac ctctgcaccg acgtggcccc cccgttgatc 12
60

gtccacaaca tacagaatgg ctgtcatggt ccaatctgta cagaatacgc catcaataaa 13
20

ttgcggcaag aaggaagcga ggagggatg tacgtgctga ggtggagctg caccgacttt 13
80

gacaacatcc tcatgaccgt cacctgcttt gagaagtctg agcaggtgca gggtgcccag 14
40

aagcagttca agaactttca gatcgaggtg cagaagggcc gctacagtct gcacggttcg 15
00

gaccgcagct tccccagctt gggagacctc atgagccacc tcaagaagca gatcctgcgc 15
60

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

acggataaca tcagcttcat gctaaaacgc tgctgccagc ccaagccccg agaaatctcc 16
20

aacctgctgg tggctactaa gaaagcccag gagtggcagc ccgtctaccc catgagccag 16
80

ctgagtttcg atcggatcct caagaaggat ctggtgcagg gcgagcacct tgggagaggc 17
40

acgagaacac acatctattc tgggaccctg atggattaca aggatgacga aggaacttct 18
00

gaagagaaga agataaaagt gatcctcaaa gtcttagacc ccagccacag ggatatttcc 18
60

ctggccttct tcgaggcagc cagcatgatg agacaggtct cccacaaaca catcgtgtac 19
20

ctctatggcg tctgtgtccg cgacgtggag aatatcatgg tggaagagtt tgtggaaggg 19
80

ggtcctctgg atctcttcat gcaccggaaa agtgatgtcc ttaccacacc atggaaattc 20
40

aaagttgcca aacagctggc cagtgccctg agctacttgg aggataaaga cctggtccat 21
00

ggaaatgtgt gtactaaaaa cctcctcctg gcccgtgagg gaatcgacag tgagtgtggc 21
60

ccattcatca agctcagtga ccccggcatc cccattacgg tgctgtctag gcaagaatgc 22
20

attgaacgaa tcccatggat tgctcctgag tgtgttgagg actccaagaa cctgagtgtg 22
80

gctgctgaca agtggagctt tggaaccacg ctctgggaaa tctgctacaa tggcgagatc 23
40

cccttgaaag acaagacgct gattgagaaa gagagattct atgaaagccg gtgcaggcca 24
00

gtgacaccat catgtaagga gctggctgac ctcatgaccc gctgcatgaa ctatgacccc 24
60

aatcagaggc ctttcttccg agccatcatg agagacatta ataagcttga agagcagaat 25
20

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
ccagatattg tttccagaaa aaaaaaccag ccaactgaag tggacccccac acattttgag 25
80

aagcgcttcc taaagaggat ccgtgacttg ggagagggcc actttgggaa ggttgagctc 26
40

tgcaggtatg accccgaaga caatacaggg gagcaggtgg ctgttaaatc tctgaagcct 27
00

gagagtggag gtaaccacat agctgatctg aaaaaggaaa tcgagatctt aaggaacctc 27
60

tatcatgaga acattgtgaa gtacaaagga atctgcacag aagacggagg aaatggtatt 28
20

aagctcatca tggaatttct gccttcggga agccttaagg aatatcttcc aaagaataag 28
80

aacaaaataa acctcaaaca gcagctaaaa tatgccgttc agatttgtaa ggggatggac 29
40

tatttgggtt ctcggcaata cgttcaccgg gacttggcag caagaaatgt ccttgttgag 30
00

agtgaacacc aagtgaaaat tggagacttc ggtttaacca aagcaattga aaccgataag 30
60

gagtattaca ccgtcaagga tgaccgggac agccctgtgt tttggtatgc tccagaatgt 31
20

ttaatgcaat ctaaatttta tattgcctct gacgtctggt cttttggagt cactctgcat 31
80

gagctgctga cttactgtga ttcagattct agtcccatgg ctttgttcct gaaaatgata 32
40

ggcccaaccc atggccagat gacagtcaca agacttgtga atacgttaaa agaaggaaaa 33
00

cgcctgccgt gcccacctaa ctgtccagat gaggtttatc agcttatgag aaaatgctgg 33
60

gaattccaac catccaatcg gacaagcttt cagaacctta ttgaaggatt tgaagcactt 34
20

ttaaaataa 34
29

TENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

<210> 5
<211> 3399
<212> DNA
<213> Homo sapiens

<400> 5
atgggaatgg cctgccttac gatgacagaa atggagggaa catccacctc ttctatatat
60

cagaatggtg atatttctgg aaatgccaat tctatgnagc aaatagatcc agttcttcag 1
20

gtgtatcttt accattccct tgggaaatct gaggcagatt atctgacctt tccatctggg 1
80

gagtatgttg cagaagaaat ctgtattgct gcttctaaag cttgtggtat cacacctgtg 2
40

tatcataata tgtttgcttt aatgagtgaa acagaaagga tctggtatcc acccaaccat 3
00

gtcttccata tagatgagtc aaccaggcat aatgtactct acagaataag attttacttt 3
60

cctcgttggt attgcagtgg cagcaacaga gcctatcggc atggaatatc tcgaggtgct 4
20

gaagctcctc ttcttgatga ctttgtcatg tcttacctct ttgctcagtg gcggcatgat 4
80

tttgtgcacg gatggataaa agtacctgtg actcatgaaa cacaggaaga atgtcttggg 5
40

atggcagtgt tagatatgat gagaatagcc aaagaaaacg atcaaacccc actggccatc 6
00

tataactcta tcagctacaa gacattctta ccaaaatgta ttcgagcaaa gatccaagac 6
60

tatcatattt tgacaaggaa gcgaataagg tacagatttc gcagatttat tcagcaattc 7
20

agccaatgca aagccactgc cagaaacttg aaacttaagt atcttataaa tctggaaact 7
80

ctgcagtctg ccttctacac agagaaattt gaagtaaaag aacctggaag tggtccttca 8
40

:NT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

ggtgaggaga tttttgcaac cattataata actggaaacg gtggaattca gtggtcaaga 9
00

gggaaacata aagaaagtga gacactgaca gaacaggatt tacagttata ttgcgatttt 9
60

cctaatatta ttgatgtcag tattaagcaa gcaaaccaag agggttcaaa tgaaagccga 10
20

gttgtaacta tccataagca agatggtaaa aatctggaaa ttgaacttag ctcattaagg 10
80

gaagctttgt ctttcgtgtc attaattgat ggatattata gattaactgc agatgcacat 11
40

cattacctct gtaaagaagt agcacctcca gccgtgcttg aaaatataca aagcaactgt 12
00

catggcccaa tttcgatgga ttttgccatt agtaaactga agaaagcagg taatcagact 12
60

ggactgtatg tacttcgatg cagtcctaag gactttaata aatatttttt gacttttgct 13
20

gtcgagcgag aaaatgtcat tgaatataaa cactgtttga ttacaaaaaa tgagaatgaa 13
80

gagtacaacc tcagtgggac aaagaagaac ttcagcagtc ttaaagatct tttgaattgt 14
40

taccagatgg aaactgttcg ctcagacaat ataattttcc agtttactaa atgctgtccc 15
00

ccaaagccaa aagataaatc aaaccttcta gtcttcagaa cgaatggtgt ttctgatgta 15
60

ccaacctcac caacattaca gaggcctact catatgaacc aaatggtgtt tcacaaaatc 16
20

agaaatgaag atttgatatt taatgaaagc cttggccaag gcacttttac aaagattttt 16
80

aaaggcgtac gaagagaagt aggagactac ggtcaactgc atgaaacaga agttctttta 17
40

aaagttctgg ataaagcaca cagaaactat tcagagtctt tctttgaagc agcaagtatg 18
00

:NT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

atgagcaagc tttctcacaa gcatttggtt ttaaattatg gagtatgtgt ctgtggagac 18
60

gagaatattc tggttcagga gtttgtaaaa tttggatcac tagatacata tctgaaaaag 19
20

aataaaaatt gtataaatat attatggaaa cttgaagttg ctaaacagtt ggcatgggcc 19
80

atgcattttc tagaagaaaa cacccttatt catgggaatg tatgtgccaa aaatattctg 20
40

cttatcagag aagaagacag gaagacagga aatcctcctt tcatcaaact tagtgatcct 21
00

ggcattagta ttacagtttt gccaaaggac attcttcagg agagaatacc atgggtacca 21
60

cctgaatgca ttgaaaatcc taaaaattta aatttggcaa cagacaaatg gagttttggt 22
20

accactttgt gggaaatctg cagtggagga gataaacctc taagtgctct ggattctcaa 22
80

agaaagctac aattttatga agataggcat cagcttcctg caccaaagtg ggcagaatta 23
40

gcaaacctta taaataattg tatggattat gaaccagatt tcaggccttc tttcagagcc 24
00

atcatacgag atcttaacag tttgtttact ccagattatg aactattaac agaaaatgac 24
60

atgttaccaa atatgaggat aggtgcccta gggttttctg gtgcctttga agaccgggat 25
20

cctacacagt ttgaagagag acatttgaaa tttctacagc aacttggcaa gggtaatttt 25
80

gggagtgtgg agatgtgccg gtatgaccct ctacaggaca acactgggga ggtggtcgct 26
40

gtaaaaaagc ttcagcatag tactgaagag cacctaagag actttgaaag ggaaattgaa 27
00

atcctgaaat ccctacagca tgacaacatt gtaaagtaca agggagtgtg ctacagtgct 27
60

NT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

ggtcggcgta atctaaaatt aattatggaa tatttaccat atggaagttt acgagactat 28
20

cttcaaaaac ataaagaacg gatagatcac ataaaacttc tgcagtacac atctcagata 28
80

tgcaagggta tggagtatct tggtacaaaa aggtatatcc acagggatct ggcaacgaga 29
40

aatatattgg tggagaacga gaacagagtt aaaattggag attttgggtt aaccaaagtc 30
00

ttgccacaag acaaagaata ctataaagta aaagaacctg gtgaaagtcc catattctgg 30
60

tatgctccag aatcactgac agagagcaag ttttctgtgg cctcagatgt ttggagcttt 31
20

ggagtggttc tgtatgaact tttcacatac attgagaaga gtaaaagtcc accagcggaa 31
80

tttatgcgta tgattggcaa tgacaaacaa ggacagatga tcgtgttcca tttgatagaa 32
40

cttttgaaga ataatggaag attaccaaga ccagatggat gcccagatga gatctatatg 33
00

atcatgacag aatgctggaa caataatgta aatcaacgcc cctcctttag ggatctagct 33
60

cttcgagtgg atcaaataag ggataacatg gctggatga 33
99

<210> 6
<211> 1584
<212> DNA
<213> Homo sapiens

<400> 6
atggcggggc gaggctctct ggtttcctgg cgggcatttc acggctgtga ttctgctgag
60

gaacttcccc gggtgagccc ccgcttcctc cgagcctggc acccccctcc cgtctcagcc 1
20

aggatgccaa cgaggcgctg ggccccgggc acccagtgta tcaccaaatg cgagcacacc 1

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
80

cgccccaagc caggggagct ggccttccgc aagggcgacg tggtcaccat cctggaggcc 2
40

tgcgagaaca agagctggta ccgcgtcaag caccacacca gtggacagga ggggctgctg 3
00

gcagctgggg cgctgcggga cggggaggcc ctctccgcag accccaagct cagcctcatg 3
60

ccgtggttcc acgggaagat ctcgggccag gaggctgtcc agcagctgca gcctcccgag 4
20

gatgggctgt tcctggtgcg ggagtccgcg cgccaccccg gcgactacgt cctgtgcgtg 4
80

agctttggcc gcgacgtcat ccactaccgc gtgctgcacc gcgacggcca cctcacaatc 5
40

gatgaggccg tgttcttctg caacctcatg gacatggtgg agcattacag caaggacaag 6
00

ggcgctatct gcaccaagct ggtgagacca aagcggaaac acgggaccaa gtcggccgag 6
60

gaggagctgg ccagggcggg ctggttactg aacctgcagc atttgacatt gggagcacag 7
20

atcggagagg gagagtttgg agctgtcctg cagggtgagt acctggggca aaaggtggcc 7
80

gtgaagaata tcaagtgtga tgtgacagcc caggccttcc tggacgagac ggccgtcatg 8
40

acgaagatgc aacacgagaa cctggtgcgt ctcctgggcg tgatcctgca ccaggggctg 9
00

tacattgtca tggagcacgt gagcaagggc aacctggtga actttctgcg gacccggggt 9
60

cgagccctcg tgaacaccgc tcagctcctg cagttttctc tgcacgtggc cgagggcatg 10
20

gagtacctgg agagcaagaa gcttgtgcac cgcgacctgg ccgcccgcaa catcctggtc 10
80

tcagaggacc tggtggccaa ggtcagcgac tttggcctgg ccaaagccga gcggaagggg 11

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
40

ctagactcaa gccggctgcc cgtcaagtgg acggcgcccg aggctctcaa acacgggttc 12
00

accagcaagt cggatgtctg gagttttggg gtgctgctct gggaggtctt ctcatatgga 12
60

cgggctccgt accctaaaat gtcactgaaa gaggtgtcgg aggccgtgga gaaggggtac 13
20

cgcatggaac cccccgaggg ctgtccaggc cccgtgcacg tcctcatgag cagctgctgg 13
80

gaggcagagc cgcccgccgg ccacccttcc gcaaactggc cgagaagctg gcccgggagc 14
40

tacgcagtgc aggtgcccca gcctccgtct cagggcagga cgccgacggt ccacctcgcc 15
00

ccgaagccag gagccctgac cccacccggt ggcccttggc cccagaggac cgagagagtg 15
60

gagagtgcgg cgtgggggca ctga 15
84

<210> 7
<211> 2544
<212> DNA
<213> Homo sapiens

<400> 7
atggagccct tgaagagcct cttcctcaag agccctctag ggtcatggaa tggcagtggc
60

agcgggggtg gtgggggcgg tggaggaggc cggcctgagg ggtctccaaa ggcagcgggt 1
20

tatgccaacc cggtgtggac agccctgttc gactacgagc ccagtgggca ggatgagctg 1
80

gccctgagga agggtgaccg tgtggaggtg ctgtcccggg acgcagccat ctcaggagac 2
40

gagggctggt gggcgggcca ggtgggtggc caggtgggca tcttcccgtc caactatgtg 3
00

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
tctcggggtg gcggcccgcc cccctgcgag gtggccagct tccaggagct gcggctggag 3
60

gaggtgatcg gcattggagg ctttggcaag gtgtacaggg gcagctggcg aggtgagctg 4
20

gtggctgtga aggcagctcg ccaggacccc gatgaggaca tcagtgtgac agccgagagc 4
80

gttcgccagg aggcccggct cttcgccatg ctggcacacc ccaacatcat tgccctcaag 5
40

gctgtgtgcc tggaggagcc caacctgtgc ctggtgatgg agtatgcagc cggtgggccc 6
00

ctcagccgag ctctggccgg gcggcgcgtg cctccccatg tgctggtcaa ctgggctgtg 6
60

cagattgccc gtgggatgca ctacctgcac tgcgaggccc tggtgcccgt catccaccgt 7
20

gatctcaagt ccaacaacat tttgctgctg cagcccattg agagtgacga catggagcac 7
80

aagaccctga agatcaccga ctttggcctg gcccgagagt ggcacaaaac cacacaaatg 8
40

agtgccgcgg gcacctacgc ctggatggct cctgaggtta tcaaggcctc caccttcicc 9
00

aagggcagtg acgtctggag ttttggggtg ctgctgtggg aactgctgac cggggaggtg 9
60

ccataccgtg gcattgactg ccttgctgtg gcctatggcg tagctgttaa caagctcaca 10
20

ctgcccatcc catccacctg ccccgagccc ttcgcacagc ttatggccga ctgctgggcg 10
80

caggaccccc accgcaggcc cgacttcgcc tccatcctgc agcagttgga ggcgctggag 11
40

gcacaggtcc tacgggaaat gccgcgggac tccttccatt ccatgcagga aggctggaag 12
00

cgcgagatcc agggtctctt cgacgagctg cgagccaagg aaaaggaact actgagccgc 12
60

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
gaggaggagc tgacgcgagc ggcgcgcgag cagcggtcac aggcggagca gctgcggcgg 13
20

cgcgagcacc tgctggccca gtgggagcta gaggtgttcg agcgcgagct gacgctgctg 13
80

ctgcagcagg tggaccgcga gcgaccgcac gtgcgccgcc gccgcgggac attcaagcgc 14
40

agcaagctcc gggcgcgcga cggcggcgag cgtatcagca tgccactcga cttcaagcac 15
00

cgcatcaccg tgcaggcctc acccggcctt gaccggagga gaaacgtctt cgaggtcggg 15
60

cctggggatt cgcccacctt tccccggttc cgagccatcc agttggagcc tgcagagcca 16
20

ggccaggcat ggggccgcca gtccccccga cgtctggagg actcaagcaa tggagagcgg 16
80

cgagcatgct gggcttgggg tcccagttcc cccaagcctg gggaagccca gaatgggagg 17
40

agaaggtccc gcatggacga agccacatgg tacctggatt cagatgactc atcccccttа 18
00

ggatctcctt ccacaccccc agcactcaat ggtaaccccc cgcggcctag cctggagccc 18
60

gaggagccca agaggcctgt ccccgcagag cgcggtagca gctctgggac gcccaagctg 19
20

atccagcggg cgctgctgcg cggcaccgcc ctgctcgcct cgctgggcct tggccgcgac 19
80

ctgcagccgc cgggaggccc aggacgcgag cgcggggagt ccccgacaac acccccacg 20
40

ccaacgcccg cgccctgccc gaccgagccg ccccttccc cgctcatctg cttctcgctc 21
00

aagacgcccg actcccgcc cactcctgca cccctgttgc tggacctggg tatccctgtg 21
60

ggccagcggt cagccaagag cccccgacgt gaggaggagc cccgcggagg cactgtctca 22
20

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
ccccccaccgg ggacatcacg ctctgctcct ggcaccccag gcaccccacg ttcaccaccc 22
80

ctgggcctca tcagccgacc tcggccctcg ccccttcgca gccgcattga tccctggagc 23
40

tttgtgtcag ctgggccacg gccttctccc ctgccatcac cacagcctgc accccgccga 24
00

gcaccctgga ccttgttccc ggactcagac cccttctggg actccccacc tgccaacccc 24
60

ttccaggggg gcccccagga ctgcagggca cagaccaaag acatgggtgc ccaggccccg 25
20

tgggtgccgg aagcggggcc ttga 25
44

<210> 8
<211> 2640
<212> DNA
<213> Homo sapiens

<400> 8
atgagtgatt actgggttgt tggaaagaag tctaactatg aagtattaga aaaagatgtt
60

ggtttaaagc gatttttttcc taagagttta ctggattctg tcaaggccaa aacactaaga 1
20

aaactgatcc aacaaacatt tagacaattt gccaaccttа atagagaaga aagtattctg 1
80

aaattctttg agatcctgtc tccagtctac agatttgata aggaatgctt caagtgtgct 2
40

cttggttcaa gctggattat ttcagtggaa ctggcaatcg gcccagaaga aggaatcagt 3
00

tacctaacgg acaagggctg caatcccaca catcttgctg acttcactca agtgcaaacc 3
60

attcagtatt caaacagtga agacaaggac agaaaaggaa tgctacaact aaaaatagca 4
20

ggtgcacccg agcctctgac agtgacggca ccatccctaa ccattgcgga gaatatggct 4
80

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

gacctaatag atgggtactg ccggctggtg aatggaacct cgcagtcatt tatcatcaga 5
40

cctcagaaag aaggtgaacg ggctttgcca tcaataccaa agttggccaa cagcgaaaag 6
00

caaggcatgc ggacacacgc cgtctctgtg tcagaaacag atgattatgc tgagattata 6
60

gatgaagaag atacttacac catgccctca accagggatt atgagattca aagagaaaga 7
20

atagaacttg gacgatgtat tggagaaggc caatttggag atgtacatca aggcatttat 7
80

atgagtccag agaatccagc tttggcggtt gcaattaaaa catgtaaaaa ctgtacttcg 8
40

gacagcgtga gagagaaatt tcttcaagaa gcctgccatt acacatcttt gcactggaat 9
00

tggtgcagat atataagtga tcctaatgtt gatgcctgcc cagaccccag gaatgcagag 9
60

ttaacaatgc gtcagtttga ccatcctcat attgtgaagc tgattggagt catcacagag 10
20

aatcctgtct ggataatcat ggagctgtgc acacttggag agctgaggtc atttttgcaa 10
80

gtaaggaaat acagtttgga tctagcatct ttgatcctgt atgcctatca gcttagtaca 11
40

gctcttgcat atctagagag caaaagattt gtacacaggg acattgctgc tcggaatgtt 12
00

ctggtgtcct caaatgattg tgtaaaatta ggagactttg gattatcccg atatatggaa 12
60

gatagtactt actacaaagc ttccaaagga aaattgccta ttaaatggat ggctccagag 13
20

tcaatcaatt ttcgacgttt tacctcagct agtgacgtat ggatgtttgg tgtgtgtatg 13
80

tgggagatac tgatgcatgg tgtgaagcct tttcaaggag tgaagaacaa tgatgtaatc 14
40

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

ggtcgaattg aaaatgggga aagattacca atgcctccaa attgtcctcc taccctctac 15
00

agccttatga cgaaatgctg ggcctatgac cccagcaggc ggcccaggtt tactgaactt 15
60

aaagctcagc tcagcacaat cctggaggaa gagaaggctc agcaagaaga gcgcatgagg 16
20

atggagtcca gaagacaggc cacagtgtcc tgggactccg gagggtctga tgaagcaccg 16
80

cccaagccca gcagaccggg ttatcccagt ccgaggtcca gcgaaggatt ttatcccagc 17
40

ccacagcaca tggtacaaac caatcattac caggtttctg gctaccctgg ttcacatgga 18
00

atcacagcca tggctggcag catctatcca ggtcaggcat ctcttttgga ccaaacagat 18
60

tcatggaatc atagatctca ggagatagca atgtggcagc ccaatgtgga ggactctaca 19
20

gtattggacc tgcgagggat tgggcaagtg ttgccaaccc atctgatgga agagcgtcta 19
80

atccgacagc aacaggaaat ggaagaagat cagcgctggc tggaaaaaga ggaaagattt 20
40

ctgattggaa accaacatat atatcagcct gtgggtaaac cagatcctgc agctccacca 21
00

aagaaaccgc ctcgccctgg agctcccggt catctgggaa gccttgccag cctcagcagc 21
60

cctgctgaca gctacaacga gggtgtcaag cttcagcccc aggaaatcag ccccctcct 22
20

actgccaacc tggaccggtc gaatgataag gtgtacgaga atgtgacggg cctggtgaaa 22
80

gctgtcatcg agatgtccag taaaatccag ccagccccac cagaggagta tgtccctatg 23
40

gtgaaggaag tcggcttggc cctgaggaca ttattggcca ctgtggatga gaccattccc 24
00

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

ctcctaccag ccagcaccca ccgagagatt gagatggcac agaagctatt gaactctgac 24
60

ctgggtgagc tcatcaacaa gatgaaactg gcccagcagt atgtcatgac cagcctccag 25
20

caagagtaca aaaagcaaat gctgactgcc gctcacgccc tggctgtgga tgccaaaaac 25
80

ttactcgatg tcattgacca agcaagactg aaaatgcttg ggcagacgag accacactga 26
40

<210> 9
<211> 3213
<212> DNA
<213> Homo sapiens

<400> 9
atgggagctg cgcggggatc cccggccaga ccccgccggt tgcctctgct cagcgtcctg
60

ctgctgccgc tgctgggcgg tacccagaca gccattgtct tcatcaagca gccgtcctcc 1
20

caggatgcac tgcaggggcg ccgggcgctg cttcgctgtg aggttgaggc tccgggcccg 1
80

gtacatgtgt actggctgct cgatggggcc cctgtccagg acacggagcg gcgtttcgcc 2
40

cagggcagca gcctgagctt tgcagctgtg gaccggctgc aggactctgg caccttccag 3
00

tgtgtggctc gggatgatgt cactggagaa gaagcccgca gtgccaacgc ctccttcaac 3
60

atcaaatgga ttgaggcagg tcctgtggtc ctgaagcatc cagcctcgga agctgagatc 4
20

cagccacaga cccaggtcac acttcgttgc cacattgatg ggcaccctcg gcccacctac 4
80

caatggttcc gagatgggac ccccctttct gatggtcaga gcaaccacac agtcagcagc 5
40

aaggagcgga acctgacgct ccggccagct ggtcctgagc atagtgggct gtattcctgc 6

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
00

tgcgcccaca gtgcttttgg ccaggcttgc agcagccaga acttcacctt gagcattgct 6
60

gatgaaagct ttgccagggt ggtgctggca ccccaggacg tggtagtagc gaggtatgag 7
20

gaggccatgt tccattgcca gttctcagcc cagccacccc cgagcctgca gtggctcttt 7
80

gaggatgaga ctcccatcac taaccgcagt cgcccccccac acctccgcag agccacagtg 8
40

tttgccaacg ggtctctgct gctgacccag gtccggccac gcaatgcagg gatctaccgc 9
00

tgcattggcc aggggcagag gggcccaccc atcatcctgg aagccacact tcacctagca 9
60

gagattgaag acatgccgct atttgagcca cgggtgttta cagctggcag cgaggagcgt 10
20

gtgacctgcc ttccccccaa gggtctgcca gagcccagcg tgtggtggga gcacgcggga 10
80

gtccggctgc ccacccatgg cagggtctac cagaagggcc acgagctggt gttggccaat 11
40

attgctgaaa gtgatgctgg tgtctacacc tgccacgcgg ccaacctggc tggtcagcgg 12
00

agacaggatg tcaacatcac tgtggccact gtgccctcct ggctgaagaa gccccaagac 12
60

agccagctgg aggagggcaa acccggctac ttggattgcc tgacccaggc cacaccaaaa 13
20

cctacagttg tctggtacag aaaccagatg ctcatctctcag aggactcacg gttcgaggtc 13
80

ttcaagaatg ggaccttgcg catcaacagc gtggaggtgt atgatgggac atggtaccgt 14
40

tgtatgagca gcaccccagc cggcagcatc gaggcgcaag cccgtgtcca agtgctggaa 15
00

aagctcaagt tcacaccacc accccagcca cagcagtgca tggagtttga caaggaggcc 15

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
60

acggtgccct gttcagccac aggccgagag aagcccacta ttaagtggga acgggcagat 16
20

gggagcagcc tcccagagtg ggtgacagac aacgctggga ccctgcattt tgcccgggtg 16
80

actcgagatg acgctggcaa ctacacttgc attgcctcca acgggccgca gggccagatt 17
40

cgtgcccatg tccagctcac tgtggcagtt tttatcacct tcaaagtgga accagagcgt 18
00

acgactgtgt accagggcca cacagcccta ctgcagtgcg aggcccaggg ggaccccaag 18
60

ccgctgattc agtggaaagg caaggaccgc atcctggacc ccaccaagct gggacccagg 19
20

atgcacatct tccagaatgg ctccctggtg atccatgacg tggcccctga ggactcaggc 19
80

cgctacacct gcattgcagg caacagctgc aacatcaagc acacggaggc ccccctctat 20
40

gtcgtggaca agcctgtgcc ggaggagtcg gagggccctg gcagccctcc cccctacaag 21
00

atgatccaga ccattgggtt gtcggtgggt gccgctgtgg cctacatcat tgccgtgctg 21
60

ggcctcatgt tctactgcaa gaagcgctgc aaagccaagc ggctgcagaa gcagcccgag 22
20

ggcgaggagc cagagatgga atgcctcaac ggtgggcctt tgcagaacgg gcagccctca 22
80

gcagagatcc aagaagaagt ggccttgacc agcttgggct ccggccccgc ggccaccaac 23
40

aaacgccaca gcacaagtga taagatgcac ttcccacggt ctagcctgca gcccatcacc 24
00

acgctgggga agagtgagtt tggggaggtg ttcctggcaa aggctcaggg cttggaggag 24
60

ggagtggcag agaccctggt acttgtgaag agcctgcaga gcaaggatga gcagcagcag 25

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
20

ctggacttcc ggagggagtt ggagatgttt gggaagctga accacgccaa cgtggtgcgg 25
80

ctcctggggc tgtgccggga ggctgagccc cactacatgg tgctggaata tgtggatctg 26
40

ggagacctca agcagttcct gaggatttcc aagagcaagg atgaaaaatt gaagtcacag 27
00

cccctcagca ccaagcagaa ggtggcccta tgcacccagg tagccctggg catggagcac 27
60

ctgtccaaca accgctttgt gcataaggac ttggctgcgc gtaactgcct ggtcagtgcc 28
20

cagagacaag tgaaggtgtc tgccctgggc ctcagcaagg atgtgtacaa cagtgagtac 28
80

taccacttcc gccaggcctg ggtgccgctg cgctggatgt cccccgaggc catcctggag 29
40

ggtgacttct ctaccaagtc tgatgtctgg gccttcggtg tgctgatgtg ggaagtgttt 30
00

acacatggag agatgcccca tggtgggcag gcagatgatg aagtactggc agatttgcag 30
60

gctgggaagg ctagacttcc tcagcccgag ggctgccctt ccaaactcta tcggctgatg 31
20

cagcgctgct gggccctcag ccccaaggac cggccctcct tcagtgagat tgccagcgcc 31
80

ctgggagaca gcaccgtgga cagcaagccg tga 32
13

<210> 10
<211> 3645
<212> DNA
<213> Caenorhabditis elegans

<400> 10
atgggtcatt cacatagtac tgggaaagaa atcaatgaca atgaactctt cacatgtgaa
60

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

gatcctgtat tcgatcaacc ggtggcgagt ccgaaatcgg agatttcgag caagttagcc 1
20

gaagaaatag aacggagcaa aagtccactc atactcgaga tgttccgtcc aacatttgac 1
80

acatttcgac cgccgaacag tgacagctcg actttccgtg gcagccagag cagagaggat 2
40

ctagtagcat gtagctcaat gaattcggta aacaacgtgc acgatatgaa tacagtttcc 3
00

tcttcatcat catcatctgc accacttttt gtagctctct atgatttcca cggtgtcggc 3
60

gaagagcagc tttcgttacg aaagggtgat caggtgcgaa ttctgggtta caacaaaaac 4
20

aatgagtggt gtgaggcacg attatactca acgagaaaaa atgatgcgag caatcagcga 4
80

aggttaggcg aaattggatg ggtgccaagt aattttattg ctccgtacaa ctctttggat 5
40

aagtacacgt ggtatcatgg caaaatctca aggagcgatt ctgaggctat actaggcagt 6
00

ggaatcactg gctcattttt ggtacgagaa agtgaaacaa gtataggaca gtatacaatc 6
60

tctgttcgcc atgatggtcg agtgtttcac taccggatca atgtagataa tacagaaaag 7
20

atgttcatca cacaagaagt caaattccgc acacttggag agttagtgca ccatcatagt 7
80

gttcacgctg atgggctgat atgtctttta atgtacccag cgagtaaaaa ggacaaggga 8
40

cgtggactgt tctcactgtc gcctaacgcg ccagacgaat gggaactaga tagatccgaa 9
00

atcatcatgc ataacaaatt gggcggtgga cagtacggag acgtgtacga gggatactgg 9
60

aaacgacatg actgcacaat tgcagtgaaa gcgttgaagg aagatgcaat gccacttcat 10
20

NT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
gaatttttag cagaagctgc tatcatgaaa gatttgcacc acaaaaacct tgttcgactg 10
80

cttggagtat gcactcacga ggcaccgttc tatattatca ccgagtttat gtgcaatgga 11
40

aatttgctcg agtacctgag gaggaccgat aaaagcttgc tgccacctat aatccttgtt 12
00

caaatggcta gtcagattgc gtccggcatg tcgtacctgg aagccagaca cttcattcat 12
60

agggatttgg ccgcaaggaa ttgcttagta tccgagcata atattgtaaa aattgccgac 13
20

tttgggttgg caagattcat gaaggaagac acctatacag cacatgctgg agccaagttt 13
80

cctatcaaat ggactgcccc agaggggctt gcattcaaca ccttcagctc taaatctgat 14
40

gtttgggcgt ttggagttct gctctgggaa attgccacgt atggaatggc tccctatcca 15
00

ggcgtcgagc tgtcaaatgt ttatgggctt ttggaaaacg ggttccgtat ggatggcccg 15
60

caagggtgcc ctccatcggt gtatcgcctt atgcttcagt gctggaactg gtctccgtcg 16
20

gatcgtcctc gtttccgaga tattcatttc aacttggaaa atctaatttc aagcaattcc 16
80

ttgaacgacg aggtgcaaaa acaattgaaa aagaataatg ataagaaact ggaaagtgac 17
40

aaaagaaggt ctaacgttag agaacgaagt gactctaaat ccagacattc ttcacatcac 18
00

gaccgtgacc gtgaccggga atctcttcat tctcggaact caaatcctga aattcccaat 18
60

agaagtttta taagaaccga cgacagtgta tcattcttca atccatcaac cacaagtaaa 19
20

gtaacgtcgt ttcgtgctca aggaccaccg ttcccaccac cgccacaaca aaacacaaaa 19
80

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
ccgaaactat tgaagtcagt tctgaatagt aacgctcgtc atgcatcaga ggagtttgag 20
40

agaaacgaac aagatgacgt ggttcctttg gccgagaaaa atgtgcggaa agcggttacc 21
00

aggctgggtg gaactatgcc gaaaggacaa aggatagatg catatttaga ctcgatgaga 21
60

agggttgaca gttggaaaga aagcactgac gctgacaatg aaggggcggg atcatcatcg 22
20

ctgagcagaa ctgtatcgaa tgattctctt gacacacttc ctctgccaga ttctatgaac 22
80

tcgagtacgt atgttaaaat gcatcctgca tccggcgaga acgttttcct gagacaaatt 23
40

cgttcaaaac tgaagaaacg aagtgagaca ccagagttgg atcatattga ttcagatact 24
00

gccgatgaaa caacaaaatc ggaaaagtca ccctttggat ctttgaataa atcttctatc 24
60

aaatatccaa ttaaaaacgc gcccgaattt agtgagaatc actctagagt cagccctgtc 25
20

ccggtgccac catctcgtaa cgcttctgta agtgtaagac ccgattcgaa agcagaagac 25
80

tcatcggatg agacaacaaa agatgttgga atgtggggtc ctaagcatgc cgtgacgcgg 26
40

aaaattgaaa ttgtcaagaa tgattcgtat ccaaatgtag aaggcgagtt gaaagcaaaa 27
00

attcgaaatt tacgtcatgt acccaaagaa gagagcaaca caagtagtca agaagatttg 27
60

ccacttgatg cgacagacaa cacaaatgac agcatcattg tgattccaag agatgaaaaa 28
20

gcaaaagttc gtcaactggt gacacaaaaa gtatctcctc ttcaacatca tcggccattc 28
80

tcactgcaat gtccaaacaa ttctacaagc tctgcaatat cgcattctga acacgcggat 29
40

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
agctcagaaa catcttcact ttccggtgtc tatgaggaac gtatgaaacc tgaacttcca 30
00

agaaaacgga gtaatggcga tacaaaagtg gtgccagtaa catggattat caatggagaa 30
60

aaggaaccca atggtatggc tcgaacaaaa tctctacgtg atattacatc aaagttcgaa 31
20

cagcttggaa cagcttccac gattgaaagt aagattgaag aagccgtccc atatcgtgag 31
80

catgcattgg aaaagaaagg aacttcaaaa cgattttcaa tgctggaagg aagtaatgag 32
40

ttgaagcatg ttgtcccacc gcgtaaaaac cgaaaccaag acgaatctgg ctcaattgat 33
00

gaagaaccag tgagcaagga catgattgta tcgttgctca aagtaatcca aaaggaattt 33
60

gtgaatcttt tcaatttggc gagctcagag atcactgatg aaaaactaca acaatttgta 34
20

ataatggctg ataatgtaca aaaacttcat tccacgtgtt ccgtctatgc agaacaaatc 34
80

tcaccgcata gtaaatttcg gttcaaagaa cttctttctc aacttgaaat ctacaatcga 35
40

caaattaaat tttcccacaa ccctcgagcg aagccagttg atgacaaact taaaatggcg 36
00

ttccaggact gtttcgacca aatcatgagg ctggtggatc gctga 36
45

<210> 11
<211> 3672
<212> DNA
<213> Caenorhabditis elegans

<400> 11
atggcaagca cgtcaggggc gcttgtcgac gacaacgtcc tcgaagtgct ccgcaaagca
60

cagttggacg catttattag tcagtttgtc ttcttattca acgtcagaag gtttgatcac 1
20

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

ttttcacatg ttcgagataa agatatgctg gaaattggta tgcaacaagt tcaaattcgg 1
80

cagctccgag agcagattct caaaatgtcc agagaaatgt ggaatcggag tgatccgaag 2
40

caagtgtaca ttcaagccga tcagtcgatg ccagcacaaa attcgattga cgagaaagca 3
00

ctgattccaa atgagcagat taaactgtac gagttgattg gcgagggctc ttttgctgtg 3
60

gtgaagcgtg gtacgtggac acagagcaat gggacgcatg tgaatgtcgc tgtcaaaatt 4
20

ctccgcgaca tttctccaaa tattatggat gatttgagag tggaagccag tcatttgctc 4
80

aagctccagc acccgtcttt gattcgcctt tacggaattg ttcgccagcc agcgatgatg 5
40

gtgtttgaac tctgtgaagg tggttcactg ctcgacagac tacgagatga caaaaaggca 6
00

attcttctgg tgtcacggct tcatgactat tgtatgcaaa ttgcgaaggc tttgcagttt 6
60

ttggagtcaa aacactgtgt acacagagat gtggcagcaa ggaatatttt gttggctaga 7
20

gacgaaagga cagtcaagat ctgtgatttt ggactcatgc gagcactaaa agaaaatgag 7
80

caaatgtaca ctatggctcc acaaaagaaa gtcccatttg cctggtgccc tccggaagca 8
40

cttcgtcatc gcaagttctc tcatgcttcc gacgtctggt cgtacggagt caccatctgg 9
00

gaggtgttca catttggcga ggagccatgg gtcggctgtc gagccatcga tgtgctcaaa 9
60

aacattgacg ccggcgagag gctggagaag cccaagtact gctcggagcg aatttatcaa 10
20

atcatgaaga attgttggaa attcaatccg gcagagcgat gcaaatttgg tgcaattcga 10
80

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

gaggacttgg tggcggccat gtttttggat gcagtggcaa gggagacgta caactctatt 11
40

caaccgggcg cactacaatt gacaaaaggg gatgaagttg ttgtggtgga gaacacaggc 12
00

caagactggt ttggtcagaa caagaagaac caaaagtttg gcacattccc ccgatcagtt 12
60

gtgtttgcgc agacgaacaa cgcggttgcg gcagcgacgg cggttacccc acagaaagtt 13
20

ccaacggcgc caacgatcag aattccaccg tcacacccac ccccagcccc gctgaaacca 13
80

ttgaacaata atacgaaaac ttcgctgaac gaccgcacgt caaaaatttc aatgcctgtg 14
40

gcaggttctt tcatccatac cggtcacgga gacccactag gaggccaatc atggggtaac 15
00

ccagctacga ttgcggacat gtatctcaag aatccagtga acggcgctcc attgtctagt 15
60

atgtcgagtg gtgcggaaat tatcgccagt aaggagttgc tcaccaatgg cggccggagc 16
20

acacaccaac ctgctgctcc atcgcctgcc gtcatgtcca agattcgagg tctttcgctt 16
80

gatttgccag aatatgatga tttcgatcga gcattcgatg atgggttttc tccgtcgaag 17
40

atcgagctgc ccagagagtt ttgtggcaat gacagcgtaa tcagtggtgg gtcgaacagc 18
00

atcggcttgg ctaacactta tgtcatggaa ccgcccaagc aggcatttga tattcgagga 18
60

aatcgagtgc tcccgccaac gaacaaggcg cctgtgctca ttccaactaa cccggcgcca 19
20

agtgtcatct cgagcacagc ttctgcagga atcacacttt ctacgaacag ttctcagatg 19
80

tttaccagtc aagaccgcca ttcgaatatg cccgcaaatc ttttccccga gcttcaacac 20
40

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

cgcctcaatc aaggaagttc aacgggaaat ggcgtccgac ctcggccagc ttcctcgatt 21
00

ggaattcaaa acaatgattt gagcatgctc aaccctcaac aaccagcgaa tattccgtgc 21
60

ctggttccaa ctccggctcc accagctcca gcacactttt ctcaaccggt gtcttcccag 22
20

agagttgcac aacaacaaca gaacactttg caaaaagcgc tgaacgatga actcaaagga 22
80

aatctgaaca aaagacctac tggcacgacg gcaccaccgt caaatgggtt caatgctcca 23
40

cgagcagacg ttgcaccggt ccaacagcga ccgatctcat cggcatctat tccagcgctc 24
00

caaccacaac ccattcaaca cattcagaag cctatccaac cgcaacaagt tcgtataccg 24
60

ccatcaacag ctcccgttca gaaaccagtt caagtctcag ctcctaccca tagtaatgtg 25
20

gcacccacaa cttcatctca agcgtctgca gatgcacgca atccgctacc tccaaaaaca 25
80

agcccaccag ttagcaacac gcctatcaca gttgctcctg ttcacgcggc accaactact 26
40

tcggcaccat caacttcggt ggtaacgaga aggccaactt caaccacagc tcaaatgtcg 27
00

gacgaggaga gacggtcaag aattgccatg gacatcagct ctgcacttcc agctcccagt 27
60

gctttgctct atggatctaa ctccacatca tcacttccgt cagcggcagt gtctacagcg 28
20

tctttctgtgc catcaactgc aagagacaat ccagtggaaa caagaccatc tcaacctcat 28
80

gttaccatgc cacccaaaaa atcttctgag ccgattctct cgtctgaggt gctccaacca 29
40

actcgtctgc catctgccac aacttcgcag gcaaaaccag tgactcaacc aatccgtcac 30
00

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

ccatcacctc cggtagccac tgttataccg actgcagtgg ttgacaaaaa gccagtttca 30
60

caaaatcaag gaagcaacgt tcctttgttt aacattacca actccagcaa cgggtaccct 31
20

cagttaaatg gatatccaaa ctatggaaac ggttttcagg cgtatggtta tggaatgaac 31
80

tatcatcaag gatatcctgg atatcaagga tacaattcat atggcaacgg aatggggcag 32
40

cttgcactga cccacaacgc cgtcacttct ttgccaccgt tggttccatc agagaacaga 33
00

ttctccggaa cagcccaacc acttggcgag tctgacatta tggagttttt gggaacacag 33
60

caacgtcaag cgggttcttc atcgcgagca gttccacctg catctgcatc cacgtcagca 34
20

gcttctggaa tcacggattt gagtatggca gataagatgg aggtgttgta tagagaagct 34
80

gattttacgc ataaaggaaa ttgtgatacc atggtttctc agtgcaacgg aaacaccgaa 35
40

caggcgttga agcttctcaa acaacaacac ttggtggata tggaacttgc aatgtcaacg 36
00

gagaccgccc gacaagcact cgaggccaga cagtatgatc tccctgcagc cgccaacatg 36
60

ttgctcggct ga 36
72

<210> 12
<211> 1335
<212> DNA
<213> Caenorhabditis elegans

<400> 12
atgtcaatta attctctttc gaacgaaacg cccactccaa caatcgagaa agaagcctac
60

ttccatggat tgatccaacg agaagatgtc ttccagctcc ttgacaataa tggcgactac 1

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
20

gtggtcagac tgtcggatcc aaagcccggc gagcctcgct cctacattct gagcgtcatg 1
80

ttcaacaata agctcgatga gaacagttcg gtgaagcact ttgttatcaa ttctgtagag 2
40

aacaaatatt ttgtgaacaa caatatgtcg ttcaacacga ttcaacaaat gctcagccac 3
00

tatcagaaga gtcgcacgga gattctcgaa gcgtgcaaga ttttgcatcc tgtgcgcaga 3
60

caattctggg agttagatca tggcaatatc gtgattgaga agaaactagg cgaaggtgct 4
20

tttggtgaag tttcctccgg agttatgaag ttcaagagag gtggaaggct ggtgaaggtt 4
80

gctgtgaagc aggtaaaaac cgatggtatc gggaaagatc aaatcaagga tttcctgatg 5
40

gaagctcgta ccatgcgaaa cctcggtcat ccaaacatcg taagattcct cggaatcgcc 6
00

gtgctgcagg agccgctgtt cctggtgatg gagctcgcga cgggcggcgc tttggatagc 6
60

tacttgaagc ataatgagtt gctgccgatt gacaagagac acgagatgct tcttcaagca 7
20

gcatggggtc tcgagtacat ccatggaaaa cccatgctgc atagggacat cgccgcgcga 7
80

aattgccttt atggagatgg gaaggttaaa atttcggatt tcggcctaac ccgtagagga 8
40

accatctacc aattgcatcc ggagacgaag tcaccaattc gatggctggc agttgaaact 9
00

atcaggacta tggtttgctc tcagaagact gacgtctggg cttacgggat tctctgctgg 9
60

gagatcttca acaacggagc cgagccgtat ccgggactga ctgccaatga ggttgctaag 10
20

caggtgactg atggataccg tatgccacca caccagttgg ctgcgccaga ggttcaagcg 10

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
80

ttgatgacga gatgctgcgc ggagaacccc aacgatcgtc caacaatgtc ggatgtcgct 11
40

cagatcttgc aacgcgtcac tggtcaagga cgtcccaact ttgcagcgat tgccaagaaa 12
00

gaggctgaag agcttctcat catgaattct cgtagtgcaa ggagaacttc acgacgtaag 12
60

ggcagtaata agaagtcggc aattccaaac ggagttttaa cacctgtcaa tagagctcaa 13
20

gaaattaagc attga 13
35

<210> 13
<211> 1689
<212> DNA
<213> Caenorhabditis elegans

<400> 13
atgttcatca gcaaagagga aatgaatcgt acttttggtg tcaaagctga gctgaattac
60

attgaaatgg ggaatgttag ctcgtactct acaaagtttc actacagagt tatggcaaac 1
20

atcgactacc tctcgttcac atggaatgct gttggaattg tacactatga agtttacgtc 1
80

gaatctgatg actcttctgt gcttcctatt gttcgaattc cattgaaagg aacggtgcca 2
40

gaatctttgc aggacttcac cgttgaatac agatgtgccg gacaccgatc cggacaattt 3
00

gctgtcagtc tatatttcac attcaaatat ggtaataagg agccgttgaa agtgaaattg 3
60

cgacaggaga agatctgcgc ttcaagggac ggacgtcgag gtctgaacgg aggctacgag 4
20

ggtcatgaag tcgacgacac tgactcaata gacaaggcat tttttgttat catttgcatt 4
80

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
gctgcggcat tcctacttat tgtggcagca acgttgatct gttatttcaa gcgctctaaa 5
40

aaagaagaca tgattccgac tcgacttcca acgtcttttc ggaattcttt gaaatctaca 6
00

aaaagcgcgc agcctttttct tctgagcaca ccgcgagatg gacctccgac tctttccgct 6
60

atttcaagcg ctccttgttc ttcgtcgtct gcgtcgggaa attcgataat cccgagcaag 7
20

ccaagaaaca ttgacgtgag acgtgcattg ttacaactct atcaagatcg agatgctttt 7
80

caatctctac ctctagatat ggagggaaca tttggagaag tgagatatgc aatttggcgt 8
40

caagtagatg acgtactgaa cggagatgtt gacgacgaag aagacacatt ctgtaaccag 9
00

gaagctgttt acaccaaaac gttgaaaaat aatgcctcac caattcagct ggatcggttt 9
60

ttgtccgacg cccttctatt ttacaacatc acacctcacc aaaacttgtc tcaagtggca 10
20

tgtgtggctt ccttcggaag attcgaccgc ccggaaactg tcacagattt tccacttgtt 10
80

tgttacagac accaaggctt tggaaacctg aagaagttcc tcaccatctg ccgacatggt 11
40

gataaaacta aaggagctca aactctccga actcatcaac tcgtctctct ggccacacaa 12
00

gtatcttctg cagtagctca tatacacaaa tatagaatag tgcataacga cattgccgct 12
60

agaaactgct tgatcgcaga agtgaatggg cgactccaag tgcaattatg cgactcggcg 13
20

ctgtcccgcg atctgttccc agctgattat cactgcttgg gtgacaatga gaacagacca 13
80

ttgaaatgga tgtctccaga agctattgca aatgagctgt actcatcggc cgctgatgtt 14
40

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
tggtcactgg gagttctact gtgggagctc atgtcgctag gaggatctcc acacgctgaa 15
00

atagaccctg aggaagtgta cacaatgatt ctcaaaggaa agcgtctgca acagccgaac 15
60

aattgtccgg atcaattata cgaagtcatg ctgtgctgtt ggagggtact cagcgaagat 16
20

cgtcctagca gtgagcaggt agttcatgga cttcgagact ttaacattca actcagtcaa 16
80

tacatctaa 16
89

<210> 14
<211> 3603
<212> DNA
<213> Drosophila melanogaster

<400> 14
atgaacaccg cgggagccac cagtcaaccg ccgcccacta aaaatgagat taactccgag
60

gagtatctca tccacgtgca tatgccgaac aagagcttca aggctgttcg gtttaatgtc 1
20

aaggagaccg ttttccatgt gatccggcgc actgtcgagg atctgggcac ggatggacgg 1
80

acgcccagca ttcagcgata tgcctgccgc atgcttaaca tgatcaccaa ggaggtgatt 2
40

tggctggcta gaagcacttc aatgcagaag gttctctcgc acatcctgac gcccggctgc 3
00

tccaacgttg actgtcccaa caaccagtcg gagttggatg aggttctatt ggagcacgga 3
60

agaaggatca ccgataatag ggtgtggcga gtggagctca gagtgcgcta cgtgccaaat 4
20

aatattcaag agctcttcga ggaggacaag gccacatgct tctattattt caatcaggtg 4
80

aaagaggact ttatccaagc caatgtcaca gccatcgaca ctgaagtggc ggtgcaactg 5
40

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

tgctgtctgg gcattcgtca ttatttcaag aacatcaccg tgaaagcacc tgacaaaaag 6
00

cagcacattg actacattga aaaggaaatc ggatttaaaa gttttcttcc acaatctgtg 6
60

atagccacat caaagccaaa gaatcttaag aaactgatcc aagtcggtta caaaaaggtc 7
20

tacaattaca acgacattga gtacttgacg cggttctttg atcttctgaa gaatatttat 7
80

ttaacgaact tcgagcagtt ctcggtaacc ctgagctcgg cgtggaatat ttctggaatt 8
40

ctacacgtcg gccctcacat tggaatctcg taccagactc atcctcaggc cagcttgaag 9
00

aacgtggctc agtttaaaga tgtggtctct attaaaacgt gcactttacc aaaggaaaaa 9
60

ctgtccaagt ctggggagaa taccacagaa ccagagcttc agaattttaa ttgcaactgc 10
20

cagaagatta aaacccaaat aaaaatatcc gcttccaaca atgtggaaga tttggttata 10
80

acgtgcaatg gtattaatac cgctgagagt attgctgacc taattgacgg ttactgccgg 11
40

ctgttatcaa aagacctaga gttcacgatt tggcatcgag agacaaacgc gtcgaacgaa 12
00

gatagcgcaa aagcattgcc caatgatgcg acgctggggt ccaataaatc aacttcaagt 12
60

cagggaaaac cgatgctgac cgatgattat gccgagattg gtttattgga gggcgagggc 13
20

gactactcta cgcccaccgt tcgaaattat gagttggaca gagccctcat aacgccgagc 13
80

gccaaaattg gtgtgggaca gtttggtgat gtgtatgtag gcacgtatac gcttccgaaa 14
40

ctgggcaagg gcaagaactt agcaggaaat ggaaaaaata gtaatagtga ccaaagaaat 15
00

:NT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

gccgattcaa ggccagatgt tatacaagtg gcgataaaga catgtaaagc taacgacgat 15
60

cctgaaaaaa ccgaaaattt tcttgccgaa gcttatatta tgcaaaaatt cgatcatccc 16
20

catattatac gcttaatcgg catttgcagc gtaatgccca tttggatagt tatggaattg 16
80

gccaaactgg gtgaattgcg tgcgtactta aagacaaaca gcgaaagatt aagccacggt 17
40

actttactga agtattgcta tcagctatcg actgctctta gttatttgga atccaaaaag 18
00

tttgttcacc gagatatagc ggcgcgtaat gtactagtca gctcaccaac gtgtgttaag 18
60

ttggctgatt ttggattatc acgttgggtt tccgatcagt cgtattatca ctcaacaccc 19
20

acagttgccc tacccattaa atggatgtcc cccgagtcaa taaactttag aagatttacc 19
80

actgctagtg atgtttggat gtttggtgtc tgcatttggg aaatactcat gctcggtgta 20
40

aagcctttcc aaggcgtcaa gaacagcgat gttatattga agctcgaaaa cggagagcgt 21
00

ctgccattgc ctcccaactg cccacctagg ttatattcgt taatgtccca atgctgggcg 21
60

tacgagccac ttaaacgacc gaatttcaag cggatcaagg aaactctgca tgaaattctg 22
20

attgaagaca gcattaattc atcggagaca ctgaagcggg agcaacgaaa agtggcttcc 22
80

atgtcctgga ttggcagtga tgacatcgac attccgccat cgaaaccttc aagggtgatg 23
40

cacgatcctg acatcactgg cttaatgcct gaaacaacgg ggctacctca gacctatatt 24
00

attgcacaaa atcccgcggt gctggccaaa ctgatgatgg agaaccaaaa acgaggcata 24
60

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

aatccagcgg cgtacaccac accagcttcg ggcattcaca atgttttggg cgaaaaacta 25
20

cgacaacagc aaaaggatag caacagcgac agcgaatggt taattcaaga agaattgcta 25
80

cggcagagat cctgctcaat acctcaagga tcgctcaatg atcatcaggc tcaaatgttt 26
40

aagcttgact tcatgtcagc tggtccttcc agtttgccgg actgctcgaa ctccagttct 27
00

cgacctatga caccaaatgc caatctttct tcactgaagt cgaaccactc atcggcggat 27
60

catttgtcca gcttgacatc tgcagaagaa cagatgggtt caaatgcacg aaacctgggc 28
20

agtgcagttc caagtcgacc acctaaccgc gcagatgacg aagtttattg cgccaccaca 28
80

ctggtggtca aatcaataat ggcgctgtca caaggtgtgg agaaagcgaa taccgagggt 29
40

tacttggaat tggttaagaa cgtgggcgtc aagttgagaa acttgctaac atcggtggac 30
00

aaaatatcta taatatttcc agcacaggcc ctcaaggaag tgcaaatggc acatcaggta 30
60

ctttcaaaag acatgcacga attggtctca gcgatgcgat tggctcaaca atatagtgac 31
20

acaacgctgg attgtgaata tcgcaagagt atgctgtctg ctgcccacgt tttggctatg 31
80

gacgccaaaa acctgtttga tgttgtcgat tcgatacgtc aacgttatca gcatctattc 32
40

ccgccatccg ccacaaaaga aacaagttgt tcgtcaagtt tcgagtcgac ttctggatct 33
00

attgtcgcag agccagttaa tgaccttggt ggttatatca agactagcac ttctggagat 33
60

ttgcttcaaa acacaggaat atatgataat gatttgcatc atagcttcaa ctcgcaattg 34
20

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

cagttgcaaa acccaaaagc cagcatcgac ttaagcggcg gtggtagtct acagcgaggg 34
80

atgagccttg gcttggacac aaccaggtcg acaaacgaac cgttgcgaat tgttgaggag 35
40

accctgggca gcccgggtga acatatgtac tgcaatacgt ccgccttgca cggccacgcg 36
00

taa 36
03

<210> 15
<211> 2772
<212> DNA
<213> Drosophila melanogaster

<400> 15
atgcttattt tctacgcgaa gtacgcattt atcttctggt ttttcgtggg aagcaatcaa
60

ggtgaaatgt tgctaatgga caaaatctct cacgataaga cgcttctcaa cgtcaccgct 1
20

tgcacccaga attgtctgga aaagggccag atggatttcc gaagctgttt aaaggactgc 1
80

aggattaatg gaacatttcc cggggctctg cgcaaggtgc aggaaaacta ccagatgaac 2
40

atgatctgcc gcacggagtc ggaaatcgtt ttccaaatag attgggtgca gcacagcagg 3
00

ggaaccgagc cggctccaaa tgccacctac ataatccggg tggatgctgt caaggacgac 3
60

aacaaagaaa ctgcgcttta cctgtctgat gacaactttc tcatcctgcc gggattggag 4
20

tccaactcta cccacaacat caccgccctg gcgatgcacg gagatggcag ctactccttg 4
80

atagcaaagg accagacctt cgccaccctc atccgaggct atcagcccag caaaatggga 5
40

gcggtgaatc tgctgcggtt tgtcccccaa ccagacgacc tgcatcacat tgctgccgaa 6

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
00

atcgagtgga agccatcggc ggagagcaac tgctatttcg acatggtgtc gtattcaacc 6
60

aacagcgtga atatggacga gccactggag gtgcagttcc gggatcgcaa aaagctgtac 7
20

aggcacacgg tggacaactt ggagtttgac aaacagtatc acgttggcgt aagaacggtg 7
80

aacataatga atcgactgga gagcgatctg cagtggctgc caatcgctgt tccaagctgc 8
40

ttggattggt atccctataa ctacacactc tgcccacccc ataagccaga gaatcttact 9
00

gtgacccaga agcagtatct gccaaatatt ttggccctga acatcacctg ggcgcgtccc 9
60

agatacctgc cggataacta tacacttcac atctttgatc tattcaaagg aggtacggag 10
20

ctaaactata cacttgacca aaacaggagc cacttctatg tacccaagat cacggtactg 10
80

ggttcccatt tcgaagtaca tttggtggcc cagtcggcag gcggaaaaaa cgtatccggt 11
40

ttgacgttgg acaaggttca tcgaggtgtg ttgctgagcg agggcaacat ggtcaagttg 12
00

gtactcttta ttatcgtgcc catatgctgc attttgatgc tgtgctccct gacgttctgc 12
60

agacgaaatc gttcggaggt tcaggcgctg caaatggacg ctaaggacgc gaaggccagt 13
20

gaatttcatc tctccctgat ggacagcagt ggcctgctgg tcaccctctc ggccaacgag 13
80

agtctggaag taatggacga gctggaggtg gagccacact cggtgctcct tcaggatgtc 14
40

ctcggcgaag gagcctttgg cttggtgcga cgtggagttt acaagaaacg ccaagtggcc 15
00

gtcaagttgc tgaaagatga accaaacgac gaggacgtat atgcgttcaa gtgcgaaatt 15

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
60

cagatgctca aggccgtggg caagcatcca aatattgtgg gtatcgtggg atactccact 16
20

cgttttagca accagatgat gttgctaatt gaatactgca gccttggaag cctgcagaac 16
80

tttttacgtg aggagtggaa gttcaggcag gagcaaaatg caattggact taagaagaac 17
40

cttgaacaga acgtggacaa ccgacggttt aaccgactcc ctagaaattc catccatgat 18
00

cgcatagagg atatcaacaa ctcgatgctg tccactgtgg aagaggagag tgaatcggat 18
60

cagacacact caagtcgatg tgagacctac accctcactc gaataaccaa tgcagccgac 19
20

aacaagggct atggcctgga ggacattgaa aacatcggtg ggagttacat tcccaaaacc 19
80

gctgaagctc caaaggatcg gccaaaacgg aagctgaagc cgcagcccaa gaaagactcg 20
40

aagcaggatt tcaaatcgga caacaagaag cgaatctttg agaacaagga atactttgat 21
00

tgcctcgact catcggatac caagccccga ataccactga aatatgcaga tttgctagac 21
60

atcgcccaac aggtggcggt gggaatggaa tttctggccc aaaacaaagt agtgcatagg 22
20

gatctggctg cccggaatgt tctaatctcc gtagatcgca gcatcaagat agcagatttt 22
80

gggctgagtc gagatgtgta tcatgagaac gtgtaccgaa agtccggagg aagtggcaag 23
40

ctgcccatca agtggctcgc gctggagtcc ctcacccacc aggtgtacac cagtcagagc 24
00

gatgtttggt cctttggtgt gctgctctat gagatcacca ctctcggtgg aatgccatat 24
60

ccgtcggtgt ctcccagtga tctcttgcag ctactgcgac aaggtcatcg gatgaagcga 25

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
20

ccggagggat gtacgcaaga aatgttttcc ctgatggaaa gctgctggag ctccgtgcca 25
80

tcacacaggc caacattttc cgcccttaaa cacagacttg gtggcatgat tttggccact 26
40

aacgatgttc cagaaaggct gaaacaactg caagctgcaa ccgagtcaaa attaaagtca 27
00

tgtgacggtc taaacagtaa agtggagcaa gtgccatgcg aggaagagct atacctagaa 27
60

cctttgaatt aa 27
72

<210> 16
<211> 5229
<212> DNA
<213> Drosophila melanogaster

<400> 16
atgttcaata tgccacgggg agtgacaaaa agtaaatcca agcgtgggaa aattaagatg
60

gaaaacgata tggcagcagc agcaacaaca acagcctgca cgcttggaca catttgtgtt 1
20

ttgtgccggc aagaaatgtt gctggataca tgttgctgcc ggcaagcagt agaagcagtt 1
80

gacagccccg caagcagtga agaagcgtat agcagtagca acagcagcag ctgtcaagca 2
40

agcagtgaaa tcagtgcgga ggaggtctgg tttctcagtc atgatgatat cgtactgtgc 3
00

cgcagaccaa aatttgacga agtggagacg acgggtaaaa agagggacgt taaatgcagc 3
60

gggcatcagt gcagcaatga atgcgacgat ggcagcacga aaaacaatcg acaacagcgc 4
20

gaaaacttca atatctttag caactgtcac aatattttgc gaacattgca atcgctgctg 4
80

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

ctgctcatgt tcaattgcgg cattttcaac aagcgacgca ggcggcagca tcagcagcag 5
40

catcatcatc attatcagca tcatcatcag cagcatcatc agcagcatca tcagcggcag 6
00

caagccaatg ttagttacac aaaattccta ttgctgctac aaacactggc agcagcaacc 6
60

acaagactga gtttaagccc taaaaactac aaacaacaac aacaactaca gcataaccaa 7
20

cagctgccac gtgccacacc gcaacaaaag caacaagaga aagataggca taagtgcttt 7
80

cactacaagc acaattactc ttactcgcct ggcattagcc ttctactctt tatcctactg 8
40

gccaacacat tggccatcca agcggtcgtg ttgccagcac atcagcagca cctgctgcac 9
00

aatgatatag ccgatggact ggataaaaca gcgctttcgg tgtcggggac gcaatcgcga 9
60

tggacaagga gcgaatcaaa cccaacaatg cgactgtcac aaaatgtaaa accttgcaaa 10
20

tccatggaca tcaggaacat ggtgtcgcac ttcaatcagc tggagaactg cacggtcatc 10
80

gagggcttcc tgctgatcga tttgataaac gacgccagcc ctctgaacag aagctttcca 11
40

aaactgaccg aggtcacaga ttatatcata atctaccgtg tgactggatt gcactcgctg 12
00

tcaaagatct ttcccaatct gagcgtcatt aggggaaaca agctgttcga cggatatgcc 12
60

ttggtcgtct actcgaattt cgacctcatg gatttgggac ttcacaagct acgatccata 13
20

accagaggcg gtgtgcggat tgagaagaat cataagctgt gctatgatag gaccatcgat 13
80

tggctggaaa ttctggcgga aaacgaaacc caactggtgg tgctgacaga gaacggcaag 14
40

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

gagaaggagt gcaggctttc caagtgcccg ggggagatca gaattgagga ggggcacgat 15
00

accacggcta ttgagggaga gcttaatgcc agttgtcagc tgcacaataa taggcgcctg 15
60

tgctggaaca gcaaactctg ccagacgaaa tgccctgaaa agtgcagaaa taactgcatc 16
20

gatgagcaca cctgctgcag ccaggattgt ttgggtggat gcgtgatcga taagaatggg 16
80

aatgagagct gcatctcctg tcgaaatgtg tctttcaaca acatctgtat ggactcctgt 17
40

ccgaaaggct attatcagtt cgacagccgc tgcgtaacgg cgaacgagtg catcacactg 18
00

acaaagtttg aaacgaacag tgtgtattcc ggtattccat acaacggaca atgtatcacc 18
60

cactgtccaa cggggtacca gaagtcagag aacaagcgca tgtgcgaacc ttgtccgggc 19
20

ggcaagtgtg acaaggagtg ctcctccggt cttatcgaca gtttggagcg tgctcgggag 19
80

ttccacggct gcaccattat aaccggaacc gagcccctta ccatcagcat taaacgtgaa 20
40

agcggcgctc acgtcatgga tgaattaaaa tatggcctgg ctgccgtcca taaaattcag 21
00

tcgtccctaa tggttcattt gacctacgga ttgaagtcct tgaaattctt tcaatcccta 21
60

actgaaatta gcggcgatcc gccgatggac gcggataaat atgctttgta tgtgcttgat 22
20

aatcgcgatc tagatgagct ctggggaccc aaccaaacgg tgttcattag gaagggcggc 22
80

gtcttctttc atttcaaccc aaaactatgt gtgtccacca ttaaccagtt gctgcccatg 23
40

ctggcctcca agccaaagtt ttttgaaaag tcagatgtgg gcgcagactc gaatggaaac 24
00

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

cgcggatcat gtggaacagc cgttctcaat gtcacattac aatcagtggg agcaaactcc 24
60

gctatgctga acgtcacgac aaaagttgaa ataggagagc cccaaaagcc gagcaatgct 25
20

acaattgttt ttaaggatcc gcgcgccttc atcggtttcg tgttttatca tatgatcgat 25
80

ccgtacggga actcaactaa aagcagtgac gatccatgcg atgatcgctg gaaggttagc 26
40

tctccggaaa agagcggggt catggtatta agcaatttga ttccgtacac taactactcc 27
00

tactacgttc ggaccatggc tatatcctcg gaattgacaa acgcggagag cgacgtgaag 27
60

aactttagga cgaatcccgg acgaccgtca aaggttacgg aggtggtagc aaccgccatt 28
20

tcagattcga aaattaacgt aacatggagc tacctagata agccttatgg cgtgctaacg 28
80

cgctatttta taaaagccaa acttataaat cggcctactc gaaacaataa ccgggattac 29
40

tgtactgaac ctctcgtcaa ggccatggaa aatgacctgc cagccacaac gcctaccaag 30
00

aaaatatcag atcctttagc aggcgactgt aagtgcgtgg agggttcgaa gaagactagc 30
60

agtcaggaat acgatgatcg taaagttcaa gcgggcatgg agtttgagaa cgcgttgcaa 31
20

aactttatat ttgttccaaa cattcggaaa agcaagaatg gatcgtctga caaatcagac 31
80

ggagcggaag gtgcagctct cgattctaat gctattccaa atggaggagc tactaaccct 32
40

tcacgtagaa ggagagacgt tgcgctcgag ccagagctcg acgatgtaga gggcagtgta 33
00

cttctacgcc atgtgcgctc catcacagac gataccgatg catttttcga aaaggacgac 33
60

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

gaaaatacct ataaagacga agaagacttg tcctccaaca aacaattcta tgaggtgttt 34
20

gccaaggaat tgccaccaaa tcaaacacat tttgtctttg aaaaactgcg ccacttcacc 34
80

cgctacgcta tcttcgtggt agcctgtaga gaagaaatcc ccagcgaaaa attaagggac 35
40

accagtttta agaagtcgct ctgcagcgat tatgacaccg ttttccaaac tacaaagaga 36
00

aagaaatttg ccgacatagt catggaccta aaagtagatt tagaacacgc caacaacacc 36
60

gagtccccag tacgggttcg ctggacgcca ccagtagatc ccaacggaga aattgtcacc 37
20

tatgaagtgg cctacaagtt gcaaaaaccc gatcaagtgg aagaaaagaa gtgcattccg 37
80

gctgctgact tcaaccagac tgccggttat ttaataaagc tcaacgaggg cctttacagc 38
40

ttcagggtgc gagccaattc aatagcggga tacggcgatt tcacggaagt cgaacatata 39
00

aaagttgagc ctccgccgag ctatgctaag gtctttttct ggctactggg aatcggccta 39
60

gcgttcctga tcgtttccct gttcggctat gtctgttacc tgcacaagag gaaggttccc 40
20

tctaatgacc ttcatatgaa cacagaggtg aatccgttct atgcgagcat gcaatacatc 40
80

ccagacgatt gggaggtgct gcgagagaac atcattcagt tggctccact aggccaggga 41
40

tcctttggca tggtgtatga gggtatcctg aagtcctttc cacccaatgg cgtggatcgc 42
00

gagtgtgcca ttaagactgt caacgaaaat gctacggatc gcgagcgaac caatttcctg 42
60

agcgaggcga gcgtcatgaa ggagttcgat acgtatcatg tcgtaagatt gctcggtgtt 43
20

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
tgctccaggg gtcagccggc tctggtggtc atggagctaa tgaagaaggg tgatcttaag 43
80

tcctatttgc gtgcccatcg tcccgaggag cgggatgagg ccatgatgac gtatcttaat 44
40

cgcatcggag tgactggtaa tgtgcagcct cctacttatg gaagaatcta ccagatggcc 45
00

attgagattg cggatggcat ggcatatttg gccgccaaga agttcgtcca tcgtgatctt 45
60

gcagctcgaa attgcatggt tgctgatgat ttgacggtga aaattggtga ctttggaatg 46
20

acccgtgaca tctatgagac ggattactat cggaagggca ctaaagggct gctgccagtt 46
80

cgctggatgc caccggagag cttgcgagat ggtgtctact ctagtgccag tgatgtattc 47
40

agctttggag tggttctctg ggaaatggcc accttagcgg ctcagccata ccagggactt 48
00

tccaacgagc aagtcctgcg ttacgtcatc gatggcggtg ttatggagag gccggaaaat 48
60

tgtcctgatt ttctgcataa actaatgcaa aggtgctggc atcataggtc ttcggcgaga 49
20

cccagttttc tggatatcat tgcgtatctc gaaccacaat gccccaattc acaatttaag 49
80

gaagtatcct tctatcactc agaggcaggt ctgcagcatc gggaaaagga gcgcaaggaa 50
40

cgcaatcagc tagatgcatt cgcggcagtc cccttggatc aagatctgca ggatcgggaa 51
00

cagcaggagg atgctaccac acctttacga atgggcgatt atcagcagaa ctcctcgttg 51
60

gatcaaccgc ccgaaagccc catcgccatg gttcctgcca tccggattca ttgcgagcag 52
20

tactcctga 52
29

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

<210> 17
<211> 2058
<212> DNA
<213> Drosophila melanogaster

<400> 17
atgaacaaat actcggcatt tatagtctgc atttcgctcg tgcttttatt tacaaaaaag
60

gatgtgggga gccataatgt ggactcaaga atatatggtt tccagcaatc atcaggtatt 1
20

tgccatattt acaatggcac catttgtcgc gatgtcttga gcaatgccca tgttttcgta 1
80

tcccccaatc tcaccatgaa cgatttggag gagcgattaa aggcagctta tggagtaatc 2
40

aaggaatcca aggatatgaa cgcaaattgc cgcatgtacg ctttgcccag cttgtgtttc 3
00

agttcaatgc caatttgccg gactccagag cgcacgaatc tcttgtactt cgccaacgtg 3
60

gccacaaatg ccaagcaact gaagaacgtc agcattcgac ggaagagaac caagtccaag 4
20

gacattaaga acataagcat attcaagaag aagtccacca tctacgagga tgtgttcagc 4
80

acagacatat cgagtaaata cccaccaacc agagagtctg agaacctaaa acgcatttgc 5
40

cgcgaagagt gcgaacttct ggagaacgag ctgtgccaga aggaatatgc cattgccaag 6
00

cgacatcccg tcatcgggat ggtgggtgtg gaggattgcc aaaagttgcc gcagcacaag 6
60

gactgcctat ccttgggcat caccatcgag gtggataaga cggagaattg ttactgggag 7
20

gatggatcga catatagagg agtggccaac gtctccgcat ccggaaagcc atgtttgcga 7
80

tggtcatggc tgatgaagga aatctccgat ttccctgaac tcatcggtca gaattattgc 8
40

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

agaaatcctg gaagcgttga aaatagtcct tggtgttttg tggactcctc acgtgaacgc 9
00

ataatcgaac tttgtgatat tccaaaatgt gcggacaaaa tatggattgc cattgtcgga 9
60

acgactgcag ccattattct aatattcata attatatttg cgataatact tttcaaaagg 10
20

agaacaatca tgcactatgg aatgaggaat attcataata tcaacacacc cagcgccgat 10
80

aaaaatatct acggaaattc gcagcttaat aacgcacaag atgctggcag gggaaatctg 11
40

ggaaatctat ccgatcacgt tgctttgaac tccaaactta tcgaaagaaa tactctgctg 12
00

aggataaacc attttacgct gcaggatgtt gagtttctgg aggagctggg cgaaggagct 12
60

tttggaaaag tctacaaggg acagctcctg cagccgaaca aaaccaccat aacagttgcc 13
20

atcaaggcgt tgaaggaaaa cgcctcggtg aaaacgcagc aggactttaa gcgcgaaatc 13
80

gaactaatct cggatctaaa gcatcagaat atagtgtgca tattgggcgt agtgctcaat 14
40

aaggagccct actgcatgct gttcgagtac atggccaatg gtgatctgca cgaattccta 15
00

atctcaaact cacccaccga aggcaagtcg ctgtcgcagt tggaattcct gcaaatagct 15
60

ctacaaatca gcgaaggaat gcagtatctg tcggcccatc attacgtaca tcgcgacttg 16
20

gcagctcgga attgcctggt aaacgagggt ctggttgtga agatatccga ttttggacta 16
80

tccagagaca tttacagctc agattattat cgagttcagt caaagtcgct attgcctgta 17
40

aggtggatgc cctcggaatc gatattgtat ggaaagttta cgaccgagag cgatgtttgg 18
00

TENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

tcctttggag tcgttctttg ggaaatatac agctatggaa tgcagccata ctacggtttt 18
60

agcaatcagg aagtaatcaa tctcatccgt tcacggcaac tgctctccgc tccggaaaac 19
20

tgtcccactg ctgtctactc gctaatgatc gagtgctggc atgagcagtc agtaaaacgt 19
80

ccaacattca cagatatttc gaaccgtctc aaaacttggc acgagggcca ctttaaggcc 20
40

agtaatccag aaatgtaa 20
58

<210> 18
<211> 1554
<212> DNA
<213> Drosophila melanogaster

<400> 18
atgggtaact gcctcaccac acagaagggc gaacccgaca agcccgcaga tcgaatcaag
60

ctggacgacc cgcccaccat cggagtcgga gtgggcgtgc cacaaatccc catgccctca 1
20

cacgccggac agccaccgga gcagatacgt ccggttcccc agatcccgga gagcgaaacg 1
80

gcaggtgcca acgccaagat ttttgtcgcc ctctacgact acgacgcccg caccgacgag 2
40

gatttgagct tccgcaaggg agagcacttg gagatactga atgacacgca gggtgactgg 3
00

tggctggcgc ggagcaagaa gacacgttcg gaaggctaca ttccatccaa ttatgtggcc 3
60

aagttgaaat caatcgaagc agaaccgtgg tacttccgca aaatcaaacg cattgaggct 4
20

gagaaaaaac ttctactgcc agagaacgag cacggtgcat ttttaattcg cgattccgaa 4
80

agccgtcaca acgactactc gctatcagtg cgcgatggcg atacggttaa gcattatcgc 5

TENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
40

atcagacaat tggacgaagg cggcttcttc atcgccaggc gcacgacatt cagaaccctt 6
00

caggagctgg tggaacacta ttcgaaggac tctgatggcc tatgcgtcaa cctctgcaag 6
60

ccgtgtgtcc agatcgagaa gcctgtaact gaggggcttt cgcaccgcac tcgcgatcag 7
20

tgggagatcg acagaacgtc tttgaaattc gtgcgcaaac tgggctccgg acagtttggc 7
80

gatgtctggg agggattgtg gaacaacaca acacctgtgg caattaaaac tctgaaatct 8
40

ggtacaatgg accccaagga tttcttagcg gaagcccaga tcatgaagaa actgcgccac 9
00

accaagctta tacagttgta cgctgtctgc actgttgagg agcctatcta tattatcaca 9
60

gagttaatga agcacggttc actgttggaa tatctccaag ccattgcagg caagggtcgt 10
20

agccttaaaa tgcaaactct gattgatatg gcagcgcaaa tagctgctgg catggcttac 10
80

ttggagtccc agaattatat tcatagggat ttagcggcgc gcaatgtact ggtaggcgat 11
40

ggaaacatcg tcaaaatcgc cgactttggt ttagctaggc tcatcaagga ggacgaatac 12
00

gaggcgcggg taggcgccag atttcccata aaatggaccg ctccagaggc tgctaactac 12
60

agcaaattct caataaaatc ggatgtttgg agctttggca ttcttctcac agaactggtc 13
20

acctacggac gcataccata tccaggcatg accaacgctg aggtgctaac gcaagtggag 13
80

cacggctatc gaatgccgca acctcccaac tgcgagccgc gcctgtatga gattatgctg 14
40

gaatgttggc acaaggaccc catgcgcaga cccacgtttg agacgctaca atggaaactg 15

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
00

gaagacttct atacatctga tcagagcgac tacaaagagg cgcaggccta ctga 15
54

<210> 19
<211> 1779
<212> DNA
<213> Drosophila melanogaster

<400> 19
atgatcaagt gcgccctgaa cgaggtggga tgcgaggagc tgccctccgg ttgcgacgat
60

gacctcaccc tggagcagaa cttcatcgag aatggctata acaacgaaca gcagagcaat 1
20

agcaatcaca gtgcctcaca gtccacgata ataacgagca cgatcaccac caccataacg 1
80

actacaacta ccacgacgcc gtccaaggaa aactcaagac tgaaattcaa agtgcccaag 2
40

atccagaaga aatcaaaggc catccgcaat acattccgct ccaagttgct caatttccag 3
00

ttgaagcgct ccaagccgtg caaacagtgc accaagagac gtcgcatcca tcccagcaaa 3
60

agtgtctttg attttgccaa agagttcgag gtggaacaac cggctggttc ggcggcggat 4
20

gagcaattct gcaactgtcc gccagctggt caaaagcctg ttaagccatc cgtccaaata 4
80

tccggccaca aagatcaccc gttcgagtcc agttctggag agctggacga gaactcggat 5
40

cgggacatcg acaacgacga ggaggaggag gatagcgcca gtgacgacgt gctcagcatg 6
00

aaggatcact gctattgcgt gcccagcctg gcggccagta tatcgctctc cacaaatcgt 6
60

ccgctttacg aggaggaatg gttccatggc gttctgccgc gcgaggaagt ggttcgattg 7
20

TENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

ctgaataacg atggtgactt cctggtccgc gaaacgattc gaaacgagga gagccagatt 7
80

gtgctcagtg tctgttggaa tggccataag cacttcattg tccagaccac cggagagggt 8
40

aatttccggt tcgagggacc accatttgcc agcatccagg agctgatcat gcatcagtat 9
00

cactcggaat tgccagtgac cgtgaaatcg ggagccatac tccgacgacc cgtttgccgg 9
60

gagcgctggg agctgagcaa cgatgatgtg gtacttctgg agaggattgg tcggggaaac 10
20

tttggggatg tctacaaggc caaactgaag tccaccaaac tggatgtggc tgtcaaaacc 10
80

tgtcgaatga ccctgcccga cgaacagaag cgtaaattcc tacaggaagg gcgcatcctc 11
40

aagcaatacg atcatccaaa tatcgtaaaa ttgattggca tttgtgtgca gaagcagccc 12
00

atcatgattg tcatggaatt ggtgctcggt ggttcgcttt taacttattt acgcaagaac 12
60

tccaatggcc tcaccactcg ccaacaaatg ggcatgtgca gagatgcggc ggcaggcatg 13
20

cgatatctgg agtccaaaaa ctgcattcat cgcgatctgg cggcgcgtaa ttgtctcgtt 13
80

gacttggagc acagtgtgaa gatctccgat ttcggaatgt ctcgcgagga agaggaatat 14
40

atagtttccg atggcatgaa acaaatacct gtgaagtgga cagctcccga ggccttgaat 15
00

ttcggcaagt acacttcgtt gtgcgatgtg tggtcctatg gcatactgat gtgggagatc 15
60

ttctccaagg gcgacacacc ctactccggc atgaccaact ccagagccag agagcgcatc 16
20

gatacgggat atcgtatgcc aacgccgaag agcacgcccg aggagatgta ccgactgatg 16
80

TENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

ctccagtgct gggcagccga cgccgaatcc cgaccgcatt tcgatgagat ctacaatgtg 17
40

gtggatgcac tgattctgcg cctggacaac agccactaa 17
79

<210> 20
<211> 2685
<212> DNA
<213> Caenorhabditis elegans

<400> 20
atgcaccatc ccaaagaaac gcttcttatc gattcatcta atccttctta ctcccacctc
60

accgagtacc gttttgataa cctgaaacgt gaagagtctc gatcgacctc acttttggc 1
20

gacaggagaa gagtgatgaa aatcctgagt ggattttccc tcattattat tgtcgttttc 1
80

atatttgcta caagtcatga acaggcgctc tctaccactg gagacctcac ttcgagtact 2
40

cagagtacta cacatggagg tgttgtcttt acatatccaa ctacaagaaa atctcccggt 3
00

aaaggatgtg tcctgaattc gcagagatca acgcctaaaa acttgaaaca gtacactgga 3
60

aacatttcag acgcttgttt agccggaata aaatcaagta actgtaagac atggctaatg 4
20

acaaatgcgg tgattttgaa atactcagac gatgttgtca gcaattgccc ttcgattttg 4
80

gaatttgtga ataaaacatc gttatcatgt tcgggtaaaa gtcagattca atatatgtat 5
40

cctcagagtg attctgcgtc aagtgattgc aatcactctt atgacttcaa ctcaaatgct 6
00

ctgaacagag caatatataa cttcaactac agcaagacct taatctccac gtcatatgcc 6
60

aatactcctg gattcgctat gtatacattt ttgctgaaga ttatgaactg tgtcaacaaa 7
20

TENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

aacggaataa aacttgacgc cggaattctc aacatttta cggacatgac ctatattgat 7
80

ttatgtgaaa gtgatgtttt catgagctcg tttccagata ctctgaacaa gcttattgag 8
40

gcggggtata ttgtcaaatt ttatttcctg aatcaaaatt tgcaagatac tcaaaaaaac 9
00

gttgaaaacg tactagctgg atgtaaatac atgaattcaa gatcgtactg cgaaattgta 9
60

gactggagct atcattcgga aaatcctaat gagtttgaaa tttgcatccc agattcacag 10
20

cccagtggga agaaagaaga ctttaattgg caacttcttc taattattgg tataccttgt 10
80

ataagtttga caatttgctg cattgcattt ttcgtttgtt gcttgaaatg tgctaaactg 11
40

aaaatggcaa tgatgagaat gaatgtattc tcaaatgata ctcaccaaaa tcctgatgaa 12
00

atggagctga aaaagagatg gatcgggatg agaaagaaat tcaataaaga tgttgagaat 12
60

ggaagttgta aagagttaaa cacccaaaaa tggtctcact tcgcatcggc gaacaattac 13
20

atggacatac aagcattggc aaatgctaat aaaaaagata tatgggaaat tgacacaaaa 13
80

aatctgctcg tccaggaaga ccatctcctt ggaaacggtg catttgcaaa cgtctataag 14
40

ggaatcgtaa aaggaaaaat accactacta gttgtaaata atagtctcaa catgaccgta 15
00

gaatcagaaa acaatggtca ctatgaagct gccatcaaga agttaccagc ccatgctgac 15
60

gagcagaacc atttggattt tttccatgaa attgatttta tgaagcgttt gggccatcat 16
20

ccacatgtca tcagcatgtt gggatgtgtg tcaaatccat atgagccatt gatcgtggtg 16
80

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

gagtattgcg cacgtggtga cctgttgaag tttttgagaa gacataaaga ttatgtgctg 17
40

atgaatcgtg tacatattga attatgtata agtatataca agttcaaatt aaaacttaga 18
00

ccgaacattg agatttcaaa aatcagtttc cagaacaaaa cagacgattg tccaattgaa 18
60

gcagacatgt gtctcagaat caaagatttg gtttctattg cttggcaagt tgccgatgga 19
20

atgtcatacc tggcatcaaa aaactttatt caccgtgatt tagctgcccg taacattctg 19
80

ctcacaaaaa gtttaactgc aaaggttagt gacttcggtc tatgtcggta tatggattca 20
40

gcactttata ccgcaaaggg gggccgtctc cccatcaaat ggatgtctgt agaagcattg 21
00

aaactgtacg aattctccac aaaaactgat gtttggtcgt ttggagtgtt gttgttcgag 21
60

attttctcca tgggagatgt tccgtatcca acaatacaac aagtagatat gctggaacac 22
20

cttctcgctg gtggccgctt gtcacagcca ttgaaatgtc cgaatgagat atttaatatc 22
80

atgcagaaat gttgggccga aaagcctgaa gacagaccag agtttaatga aatgagagga 23
40

gaaatcacag tgatgttgaa cttggacgat gaaagttatg gatatcttag cgtcgagtca 24
00

cagggtggtc caaagtatac acaattaaca atgcaagatt caaaggaaac agctccatgc 24
60

tccactcctg gaggatcaca agatatggac gaagacgggg attatgatag tggctcagaa 25
20

ggccactcgc aaggaacttg tgctcagctc gaccaggttt tgactgagag atttggtgaa 25
80

gaacagaaga aggaaatcaa gcaaatcttt tgtgagatca cttcgaaatc aatgcgaggc 26
40

TENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

aaacgccgtc aatcgaattc tacagtcagc acgtatcaat cttga 26
85

<210> 21
<211> 2376
<212> DNA
<213> Caenorhabditis elegans

<400> 21
atgtttcagg agaatgcagt caccaattgg gaatgtcaaa tcgaaagatt cgtgatgagc
60

aaatctcggc gtcttcgagt ttcgacttgc aaagcactgg acctcaacat gctcggtaag 1
20

tggtttggga actactcatt tgaaattcgt actacagctc atcaagaatc tggaagtggt 1
80

gcctggtgtc cgaagaatca aataaactct ctcagcaaag aatggttgca gatttcgttt 2
40

tccgtggata cagtaataac ttctgtggag acccagggac gatttgacga cggacgtgga 3
00

atggagtatg cgaccgcatt caaaattcag tactggcgac cttcgctaaa cgcatgggca 3
60

tcttataaag acgattttga gctagagaca attcctgcta ataatgacac ggagcacgca 4
20

atccggcgac atcttgaccg ggcaatcata gcaagaagaa tcagaattgt tccagtttca 4
80

aattccacca gaactgtttg catgagagtt gaagttttcg gatgcccatt tgatgatagt 5
40

ctcgtgtttt acaatgtcga tcaaggcgat ttgcaatctg gcatctctta tcacgacttt 6
00

tcctacgatg gtaatctcgc caactctcca cacttaaccg gcggtattgg gaagttatac 6
60

gacggcgaag tgggaaaaaa caatgtattt gttaatcacc acaaatgggt tggatggaga 7
20

cgtaaaagaa atggcaatgt gaagttggca tttgagtttt ccgaattgag aaatatatca 7

'ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
80

gggattttga ttcatacgtc gaacgagttc aaaaagagcg caaaggcatt ttcctcggct 8
40

actgtgctat tttcgataaa tggaaaagac ttctcagaca ccatcgtaca cttcaataat 9
00

ccggaagata ccgaatcaga ggtacctcga tggataagga ttccagtgaa caatcggatt 9
60

gccaaagttg caaagattcg tcttaacttt ggaactgact ccgactggct gttcatttct 10
20

gaagtgaatt ttgaatcaaa tcacacaaat attgagcttc tcaatgatga cgtggttatt 10
80

cccgattcgg tttcatattt ctccgtaacc gagcacgatg acggaactag catgtttgct 11
40

ttcattatct tcttcttcat gttcctcatc gtggcagtca ttattctgac agttctctac 12
00

cgtaaacgcg agtatcgtgt gaaagcatcg tctccatctc caaatgcgaa acgggaaatt 12
60

ctgttgacaa ttgacggaaa caccatcaag catcacgttt ctccgtcaac ctatcaaatg 13
20

gctcgcgata atcttcagaa tgcgttgatt gagaaaatgc ccatgtcacc gattataagc 13
80

gattacgctg aaccggacat tagtgtttgc tccgatgtca ccgccaacac tccattgctc 14
40

tatggaattg atggtccata tgatacacag aagagaagca acccttttgtc atctatggta 15
00

aaatactccg attatggaga ggtttattgc acaacacttc cggaaattgc tcgagacaag 15
60

ttgatttgcg tgagcagaat tgggcaagga gagtttggtg aagtcgattt gtgtcagctt 16
20

gaaaaccgaa aagttgcggt caaaaaactt catggaatca gtcaagccga cgagttttct 16
80

tttcatagag aaattcgagt attaggaagt ctcaaacatc cgaacgtagt tgaagtcgtc 17

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
40

ggagtatgca ctatacaaaa accaatactc tgtatcatgg aatatatgga aaatggcgac 18
00

ttgaaatcct acattttgaa aaaccctact atacaaacct cccaatgcat ctcaatttgc 18
60

acacagcttg ccgcaggact tgcctatttg gaatcatgta attttgtgca tagagatatt 19
20

gctgctcgaa attgccttgt tgacggagaa ggcaatgtaa aaattgccga tttcggaatg 19
80

gcccgatctc tttattctca agaatattac aaagttgagg gaaagtttgt gctcccgatt 20
40

cgctggatgg catgggaagc tttgctactc ggcaaatttt ccactgccag tgatgtttgg 21
00

ggattcggag ttaccatgtg ggagatcttc tcgctgtgct ccgaaaaacc atactccgat 21
60

atgacagatg atgatgtggt ggagaatctt cagagcatga gctctactgg atcattaaag 22
20

caagttcttt cccgaccaag gatgtgtcca tcaaagttgt acaacgagca aattcttccg 22
80

tgctggaact atgagagcag tcgccgaccc agtttcgaga acgtccatct tcacctccag 23
40

tcattggtgc acacttctcc tcatattcat ttttaa 23
76

<210> 22
<211> 3390
<212> DNA
<213> Mus musculus

<400> 22
atgggaatgg cctgccttac aatgacagaa atggaggcaa cctccacatc tcctgtacat
60

cagaatggtg atattcctgg aagtgctaat tctgtgaagc agatagagcc agtccttcaa 1
20

TENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

gtgtatctgt accattctct tgggcaagct gaaggagagt atctgaagtt tccaagtgga 1
80

gagtatgttg cagaagaaat ttgtgtggct gcttctaaag cttgtggtat tacgcctgtg 2
40

tatcataata tgtttgcgtt aatgagtgaa accgaaagga tctggtaccc acccaatcat 3
00

gtcttccaca tagacgagtc aaccaggcat gacatactct acaggataag gttctacttc 3
60

cctcattggt actgtagtgg cagcagcaga acctacagat acggagtgtc ccgtggggct 4
20

gaagctcctc tgcttgatga ctttgtcatg tcttaccttt ttgttcagtg gcggcatgat 4
80

tttgtccacg gatggataaa agtacctgtg actcatgaaa ctcaggaaga gtgtcttggg 5
40

atggcggtgt tagacatgat gagaatagct aaggagaaag accagactcc actggctgtc 6
00

tataactctg tcagctacaa gacattctta ccaaagtgcg ttcgagcgaa gatccaagac 6
60

tatcacattt taacccggaa gcgaatcagg tacagatttc gcagattcat tcagcaattc 7
20

agtcaatgta aagccactgc caggaaccta aaacttaagt atcttataaa cctggaaacc 7
80

ctgcagtctg ccttctacac agaacagttt gaagtaaaag aatctgcaag aggtccttca 8
40

ggtgaggaga tttttgcaac cattataata actggaaacg gtggaattca gtggtcaaga 9
00

gggaaacata aggaaagtga gacactgaca gaacaggacg tacagttata ttgtgatttc 9
60

cctgatatta ttgatgtcag tattaagcaa gcaaaccagg aatgctcaaa tgaaagtaga 10
20

attgtaactg tccataaaca agatggtaaa gttttggaga tagaacttag ctcattaaaa 10
80

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

gaagccttgt cattcgtgtc attaattgac gggtattaca gactaactgc ggatgcgcac 11
40

cattacctct gcaaagaggt ggctccccca gctgtgctcg agaacataca cagcaactgc 12
00

cacggcccaa tatcaatgga ttttgccatt agcaaactaa agaaggcggg taaccagact 12
60

ggactatatg tgctacgatg cagccctaag gacttcaaca aatactttct gacctttgct 13
20

gttgagcgag aaaatgtcat tgaatataaa cactgtttga ttacgaagaa tgagaatgga 13
80

gaatacaacc tcagcgggac taataggaac ttcagtaacc ttaaggacct tttgaattgc 14
40

taccagatgg aaactgtgcg ctcagacagt atcatcttcc agtttaccaa atgctgcccc 15
00

ccaaagccaa aagataaatc aaaccttctc gtcttcagaa caaatggtat ttctgatgtt 15
60

cagatctcac caacattaca gaggcataat aatgtgaatc aaatggtgtt tcacaaaatc 16
20

aggaatgaag atttaatatt taatgaaagt cttggccaag gtacttttac aaaaattttt 16
80

aaaggtgtaa gaagagaagt tggagattat ggtcaactgc acaaaacgga agttcttttg 17
40

aaagtcctag ataaagcaca taggaactat tcagagtctt tcttcgaagc agcaagcatg 18
00

atgagtcagc tttctcacaa gcatttggtt ttgaattatg gtgtctgtgt ctgtggagag 18
60

gagaacattc tggttcaaga atttgtaaaa tttggatcac tggatacata cctgaagaag 19
20

aacaaaaatt ccataaatat attatggaaa cttggagtgg ctaagcagtt ggcatgggcc 19
80

atgcattttc tagaagaaaa atcccttatt catgggaatg tgtgtgctaa aaatatcctg 20
40

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

cttatcagag aagaagacag gagaacgggg aacccacctt tcatcaaact tagtgatcct 21
00

ggcattagca ttacagttct accgaaggac attcttcagg agagaatacc atgggtacct 21
60

cctgaatgca ttgagaatcc taaaaatctc aatctggcaa cagacaagtg gagcttcggg 22
20

accactctgt gggagatctg cagtggagga gataagcccc tgagtgctct ggattctcaa 22
80

agaaagctgc agttctatga agataagcat cagcttcctg cacccaagtg gacagagtta 23
40

gcaaacctta taaataattg catggactat gagccagatt tcaggcctgc tttcagagct 24
00

gtcatccgtg atcttaacag cctgtttact ccagattatg aactactaac agaaaatgac 24
60

atgctaccaa acatgagaat aggtgcccta gggttttctg gtgcttttga agacagggac 25
20

cctacacagt ttgaagagag acacttgaag tttctacagc agcttggcaa aggtaacttc 25
80

gggagtgtgg agatgtgccg ctatgacccg ctgcaggaca acactggcga ggtggtcgct 26
40

gtgaagaaac tccagcacag cactgaagag cacctccgag actttgagag ggagatcgag 27
00

atcctgaaat ccttgcagca tgacaacatc gtcaagtaca agggagtgtg ctacagtgcg 27
60

ggtcggcgca acctaagatt aattatggaa tatttaccat atggaagttt acgagactat 28
20

ctccaaaaac ataaagaacg gatagatcac aaaaaacttc ttcaatacac atctcagata 28
80

tgcaagggca tggaatatct tggtacaaaa aggtatatcc acagggacct ggcaacaagg 29
40

aacatattgg tggaaaatga gaacagggtt aaaataggag acttcggatt aaccaaagtc 30
00

TENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

ttgccgcagg acaaagaata ctacaaagta aaggagccag gggaaagccc catattctgg 30
60

tacgcacctc aatccttgac ggagagcaag ttttctgtgg cctcagatgt gtggagcttt 31
20

ggagtggttc tatacgaact tttcacatac atcgagaaga gtaaaagtcc acccgtggaa 31
80

tttatgcgaa tgattggcaa tgataaacaa gggcaaatga ttgtgttcca tttgatagag 32
40

ctactgaaga gcaacggaag attgccaagg ccagaaggat gcccagatga gatttatgtg 33
00

atcatgacag agtgctggaa caacaatgtg agccagcgtc cctccttcag ggacctttcg 33
60

ttcgggtgga tcaaatgcgg gacagtatag 33
90

<210> 23
<211> 3246
<212> DNA
<213> Mus musculus

<400> 23
atggcacctc caagtgagga gacacctctg atccctcagc gctcttgcag cctctcatcc
60

tcagaggcag gagccctgca tgtgctcctt cctccccggg gacctgggcc tccccagcga 1
20

ttgtcattct cttttgggga ctacttggct gaggatttat gtgtgcgagc tgccaaggcc 1
80

tgtggcatcc tgcctgttta tcattcgctt ttcgctctgg ccactgagga cttctcttgc 2
40

tggtttcccc caagccacat cttctgcata gaggacgtgg acactcaagt cttggtctac 3
00

aggctacgct tttatttccc tgactggttt gggctggaga catgtcaccg ctttgggctg 3
60

cgcaaagatt tgaccagtgc catccttgac ttacatgttt tagaacatct ctttgctcag 4
20

ENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

caccgcagtg acctggtgag tgggcgcctc ccggtgggcc ttagcatgaa ggagcaggga 4
80

gagttcctga gcctggccgt gctggacttg gcccagatgg ctcgtgagca ggcccagcgc 5
40

ccaggagagc tgctgaagac ggtcagttac aaagcctgtc tgccgcccag cctgcgcgat 6
00

gtgatccagg gccagaactt cgtgacacgc aggcgcatcc gcaggaccgt ggtcttggcg 6
60

ctgcgcgtgt ggtcgcctgc caggccgacc gctacggctc atggccaagt atatctggac 7
20

ctggagcggc tacatccagc ggccaccacc gagaccttcc gtgtggggct cccgggcgcc 7
80

caggaggagc cggggcttct gcgtgtggcg ggggacaacg gcatctcctg gagctccggg 8
40

gaccaggagc ttttccagac cttctgtgac tttccggaaa tcgtggatgt cagcatcaag 9
00

cagcccacgt gtgggtccgg cagggagcac cggctggtca ctgtcaccag gatggacggc 9
60

cacatcctgg aagcggagtt tccggggctg cctgaggcgc tgtctttcgt ggccctcgtg 10
20

gatgggtact tccgcctgat ctgcgactcc aggcattatt tctgcaagga ggtggcggcg 10
80

ccacggctgc tggaggagga ggcggagctg tgccatggac ccatcacgtt agactttgcc 11
40

atccacaagc tgaaggccgc tgcgtccctc ccaggcacct atattctccg ccgcagcccg 12
00

caggactatg acagctttct tcttaccgcc tgcgtccaga ctcctcttgg ccccgactac 12
60

aagggctgcc tcatccgcca ggaccccagc ggggctttct ccctggttgg cctcagcagc 13
20

cccacagaag cctgcgggac gtgcttgcag tgctggaatt ctgggctgcg agtagacggt 13
80

TENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

gctgccctga acctaacatc ctgctgcgct cccagaccca aggaaaagtc caatttgatc 14
40

gtggtgcgaa ggggctgcac ccccgcgcct gcccctggct gctccccgtc ctgctgtgcg 15
00

ctgacacagc tgagcttcca cacaattcca acggacagcc tgggacacga gaacctgggt 15
60

cacggttctt ttaccaagat cttccgtggc cgcaggcggg aggtcgtgga tggtgagaca 16
20

catgactcgg aagtcctcct gaaggtcatg gactccagac atcggaactg catggagtct 16
80

tttctggaag ccgcaagctt gatgagccaa gtatcctacc cgcacctggt gttactgcac 17
40

ggcgtctgca tggctggaga cagcatcatg gtgcaggaat ttgtgtatct aggagcaatt 18
00

gacatgtacc tgcgcaagcg tggccacctg gtgtcagcca gctggaaact gcaggtgacc 18
60

aagcagctgg catatgccct taactacttg gaggacaaag gccttcctca cggcaacgtc 19
20

tcagcacgga aggtgctcct ggctcgtgag gggggtgatg ggaatccacc tttcattaag 19
80

ctgagtgatc ctggtgtcag tcccactgtg ctgagcctgg aaatgctcac cgacagaata 20
40

ccctgggtgg cccccgaatg tctccaggag gctcagacac tctgcttgga ggctgacaag 21
00

tggggctttg gagccaccac gtgggaggtg ttcagcgggg gacccgccca catcacctcg 21
60

ctggagcccg ccaaaaagct gaagttctat gaggaccagg gacagctgcc cgctctcaaa 22
20

tggacagaac tggcgggact tatcacacag tgcatggcgt atgatcctgg ccggcgcccc 22
80

tccttccgag ctatcctcag agacctcaac ggcctcatta catcagatta cgagctcctc 23
40

TENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

tcagacccca cacctggcat cccgagtcct cgagatgagc tgtgcggtgg cgcccagctc 24
00

tatgcctgcc aggacccccgc catattcgag gagagacacc ttaagtacat ctctttgctg 24
60

ggcaagggca actttggcag cgtggagctg tgccgctatg acccccctgga caatacggga 25
20

cccctggtgg cagtgaaaca gctacagcac agcgggccag accagcagag ggacttccag 25
80

cgggagattc agatccttaa ggctctgcac agcgacttca tcgtcaagta ccggggagtc 26
40

agctatgggc caggtcgcca gagcctgcgg ttggtgatgg agtacctgcc cagcggctgc 27
00

ctgcgagact tcctgcagcg ccatcgcgcg gccctgcaca ccgaccgcct actgctgttc 27
60

gcttggcaga tctgcaaggg catggagtac ctgggtgcgc gccgctgcgt acaccgtgac 28
20

ctggctgcgc gcaacatctt ggtggagagc gaggctcatg tgaagatcgc ggactttggc 28
80

ctcgctaagc tgctgcccct gggaaaggac tactacgtgg tccgcgagcc tggccaaagc 29
40

cccatctttt ggtatgcccc ggagtcccta tctgacaaca tcttctcccg ccaatctgac 30
00

gtgtggagct tcggagtggt gttgtacgag ctcttcacct actgcgacaa gagctgcagc 30
60

ccatccgctg agttcctgcg catgatgggg cctgagcgtg aaggaccccc gctctgccgc 31
20

ctcctggagc tgctggcaga gggccgacgc ctcccaccac ctcccacctg ccccaccgag 31
80

gttcaggagc tcatgcagct gtgcgtggcg cccagccgca cgaccggcca gccttcggca 32
40

ccctga 32
46

TENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

<210> 24
<211> 1518
<212> DNA
<213> Mus musculus

<400> 24
atggcaaggc gaagctcccg ggtctcctgg ctggcctttg aaggctggga atctagggac
60

ctgcctcggg tgagccctag attgttcgga gcttggcacc ccgcgcctgc tgcagctagg 1
20

atgccaacgc gctgggcccc tgggactcaa tgcatgacca agtgtgagaa ctctcgcccc 1
80

aagcccggtg agctagcctt tcgaaagggt gacatggtga ccatcttgga ggcctgtgag 2
40

gacaagagct ggtaccgagc caagcaccat ggcagtgggc aggaagggct gctggcggcc 3
00

gctgctctgc gacagcggga ggccctctcc acagacccca agctcagcct catgccatgg 3
60

tttcatggca agatctccgg ccaggaagcc atacagcagc tgcagccacc cgaggacggg 4
20

ctgttccttg tgagggaatc agctcgtcac cctggagact atgtcttgtg tgtcagtttc 4
80

ggccgtgacg tcatccacta ccgtgtttttg catcgagatg ggcacctcac catcgatgag 5
40

gccgtgtgtt tctgtaacct gatggacatg gtggagcact acaccaagga caaggggcc 6
00

atctgcacca agctggtgaa gccaaggagg aaacagggcg caaagtctgc agaggaggag 6
60

ctcgccaagg ctggctggct actcgacctg cagcatctga ctctgggagc acagattgga 7
20

gaggggagt ttggagccgt cctacagggt gagtacctgg gacagaaggt ggctgtgaag 7
80

aatatcaagt gtgatgtgac agcccaggcc ttcctggatg agacggctgt gatgacgaag 8

TENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND
40

ctgcagcaca ggaacctagt gcgactcctg ggtgtgatcc tgcaccacgg cttgtacatt 9
00

gtcatggagc acgtgagcaa gggcaacctg gtgaacttcc tgcgcacgcg gggccgtgct 9
60

cttgtgagca cctctcagct tctgcagttt gctcttcatg ttgctgaagg catggaatac 10
20

ctggagagca agaagctggt gcaccgggac ctggctgctc ggaacatcct ggtctctgag 10
80

gacttggtgg ccaaggtcag tgactttggc ttagccaagg cagagcgcaa ggggctggac 11
40

tcaagccggc tgccagtcaa gtggacggca cctgaggctc tcaaaaacgg gcggttctcc 12
00

agcaagtcgg atgtctggag ttttggggtg ctgttgtggg aagtcttctc ttatggaaga 12
60

gccccatacc ccaagatgtc gctaaaggag gtttcagagg ctgtggagaa gggttaccgc 13
20

atggagcccc ccgatggctg cccaggctct gtgcacaccc tcatgggtag ctgctgggag 13
80

gcagagcctg cgcgccgacc acccttccgc aaaatagtgg agaagctggg ccgtgagctc 14
40

cgcagtgtgg gtgtctcggc ccccgctggg ggacaggagg ctgagggctc agctcccaca 15
00

cggagccagg acccctga 15
18

<210> 25
<211> 1490
<212> DNA
<213> Mus musculus

<400> 25
tggagccctt cctcaggaag cggctcactt tcttgtcctt tttctgggat aagatatggc
60

TENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

cagcggatga atcggaggaa gacatcccca ggatccaggg acacgacgac aacccagtgc 1
20

cggagcaagc cgctgccgtt gaaccttgta gcttcccagc cccacgcgcc cgactcttcc 1
80

gcgcgctcta cgacttcact gctcgatgtg cagaggaact gagcgtcagc ggtggggaca 2
40

gactctacgc cctcaaggag gaggggact acatctttgc ccaaaggctc tctggtccac 3
00

ccagcaccgg actagttcct gtcacctacc ttgccaaggc taccccggag ccgccctcag 3
60

accaaccttg gtacttcagt gggatcagca gggctcaggc ccagcagttg ctcttgtctc 4
20

ctgccaatgc accaggggcc ttcctcatcc ggcccagcga aagcagcatc gggggctatt 4
80

ctctatcagt cagggcccag gccaaagtct gccactaccg catctgcatg gcacccagtg 5
40

gcagcctcta tctgcaggag ggccaactct tccccagcct ggatgcactg ctggcttact 6
00

acaagaccaa ctggaagctg atccagaacc ctctgctgca gccctgcata ccccagatac 6
60

ccttggttca ggacgagtgg gaacgaccac gttcagaatt tgtcttcgga agaaagctgg 7
20

gtgaaggttt cttcggggag gtgtgggaag gcctgtggct gggctctatc cctgtggcag 7
80

tgaaggttat caaatcagct gacatgaagc tggcagacct caccaaggag attgaggcac 8
40

tgaagagctt gaggcatgag aggctgatcc ggctgcacgc tatatgttcc ctcggtgaac 9
00

ctgtgtacat cgttactgaa ctcatgggca agggcaactt gcaagtctac ctgggcagct 9
60

ctgagggaaa ggccctgagc ctgccccatc tactgggatt tgcctgccag gtagctgagg 10
20

TENT OR GRAFT COATED OR IMPREGNATED WITH PROTEIN TYROSINE KINASE INHIBITORS AND

gcatgagcta cctggaggag cggcgtgtcg tccaccggga cttggctgcc aggaacgtgc 10
80

tggtgggtga tgacctcacc tgcaaggtag ctgattttgg cctggccaga ctgctcaagg 11
40

atgatgtcta ctccccaagc agtggctcca agatccctgt caagtggacg gcacctgagg 12
00

ctgctaatta ccgtgtcttt tcccaaaagt cagatgtctg gtcctttggc atcctgctgt 12
60

atgaggtctt cacttatggc cagtgtccct atgaaggaat gaccaaccat gagacgctac 13
20

agcagattag tcgtggatac cggctgccac gcccagctgt ctgcccagca gaggtctatg 13
80

tgctcatggt agagtgctgg aagggcagcc ctgaggagcg tcccaccttt gccatactga 14
40

gggagaagct gaatgccata aacagacgcc tccatctggg cctcacgtga 14
90